JOURNAL OF THE
American Geriatrics Society
Official Journal of the American Geriatrics Society

Volume IX *March, 1961* Number 3

TREATMENT OF CORONARY DISEASE, WITH SPECIAL REFERENCE TO OLDER PEOPLE*

ARTHUR M. MASTER, M. D.†

New York, N. Y.

Various methods have proved successful in the treatment of coronary disease. My experience in this field, over a period of almost forty years, derives from the examination and treatment of a large number of patients.

Arteriosclerotic heart disease in older people is much like that in men and women aged 40 or 50 years, but there are some real differences. Angina pectoris occurs in much the same way. Status anginosus and acute coronary occlusion appear to be less common, perhaps because such patients are too sick to survive to an advanced age, or because people aged 70 and over form a small part of the population. However, hypertension, enlarged hearts, and heart failure are often found. More aortic stenosis is seen, and a prolonged systolic murmur over the mitral area is heard more frequently. Both conditions probably are indicative of the valvular arteriosclerotic calcification that accompanies aging. Diabetes may be present. As in a younger person, the combination of hypertension and diabetes in an older patient with coronary disease bespeaks a more serious widespread arteriosclerosis and a very serious prognosis.

Acute coronary disease is manifested clinically in three distinct forms: *1) angina pectoris, 2) coronary insufficiency without occlusion,* and *3) coronary occlusion.* Angina pectoria occurs because of a transient imbalance between the myocardial demand for blood and oxygen, and their supply. Acute coronary insufficiency without occlusion represents a more prolonged and intense ischemia, which results in a physiologic dysfunction of the subendocardium, or an anatomic injury to it. A patient with acute coronary insufficiency is sick; he is kept at home or in the hospital. Acute coronary occlusion signifies complete obstruction of an artery with a transmural infarction of the left ventricle.

ANGINA PECTORIS

Diagnosis

There are exceptions to the characteristics of the chest or arm pains which have always been associated with angina pectoris. Classically, the pain or pressure

* Presented at the 17th Annual Meeting of the American Geriatrics Society, Americana Hotel, Miami Beach, Florida, June 9 and 10, 1960.

† Consultant Cardiologist, The Mount Sinai Hospital, New York, N. Y., and The Englewood Hospital, Englewood, N. J.; Consultant in Cardiovascular Disease, U. S. Marine Hospital, Staten Island, N. Y.

has been described as squeezing or constricting in character and radiating to the jaw and left arm; it has been in the substernal region, precipitated by effort or by effort following meals, and by cold, and relieved instantly by elimination of the precipitating factor or by the use of nitroglycerin. However, in significant coronary disease, the pain may not be precipitated by effort nor relieved by nitroglycerin, and it may have other atypical features. Also, noncardiac conditions may exhibit one or more of the allegedly characteristic qualities usually associated with severe classic coronary disease. (Patients, especially older ones, may have severe coronary disease with hypertensive enlarged hearts and extremely abnormal electrocardiograms, yet have no pain or pressure sensations in the chest or arm.)

Mistakes in diagnosis occur frequently. The electrocardiogram may be normal in the presence of severe coronary disease. Hence, it should not be the sole criterion. A test of heart function, such as the Master "2-step" exercise test, aids in establishing a diagnosis. Can this test be used in older people? My oldest patient on whom this test has been performed is 99 years of age. He had chest pain and an abnormal electrocardiogram twenty-five years ago. He has been completely well for a score of years. Both his resting 12-lead control and his "2-step" electrocardiograms have been consistently normal. He travels by subway. He spends five hours in the courts reviewing litigation cases and interviewing witnesses; at night, he works three hours; that is a total of eight hours a day. Over the week-end, he spends another ten to twenty hours on his work. For recreation, he walks. He does a fine job as a referee for the courts.

Status anginosus. In this condition, the patients are severely ill. They are usually persons between 35 and 65 years old. It is rare to see one at an older age, because they do not live long enough. Nevertheless, I have seen status anginosus in 2 women who were 80 years old. The patient who suffers 20 to 60 epsiodes of chest pain per day may have had the condition for many years.

Treatment

Psychologic considerations. In treating angina pectoris, the importance of the patient's psyche cannot be overemphasized. Reassurance and encouragement, constantly repeated, are essential in order to prevent cardiophobia and cardiac crippling. In the overanxious patient, a vicious cycle develops—chest pain and apprehension, apprehension and chest pain. The first step in treatment, therefore, is an attempt to improve the patient's outlook and to stimulate his hope by constant expressions of optimism.

The term "angina pectoris" should be avoided. It tends to instill a feeling of terror, or even imminent death. In an optimistic approach, the patient should be led to speak of chest pain or discomfort, and not angina; if the term "angina pectoris" has been employed previously, the patient should be told that it merely means pain or constriction around the chest and that there are many causes, such as arthritis.

Old people love life as much as young people. It might be assumed that an old person has lived a rich life and therefore is prepared to meet his Maker. This

is not true. He is as fearful as, if not more apprehensive, at age 90 than a man at age 40 or 50. He becomes just as panicky and hysterical, and just as discouraged as his younger counterpart.

Nitroglycerin should be used without hesitation for the relief of anginal pain, and, in fact, in anticipation of it. A dose of $\frac{1}{200}$ gr. usually relieves the chest or arm pain or pressure, but another tablet should be taken within one to five minutes if the symptom does not disappear immediately. More than two tablets should never be taken within one hour. If the pain or pressure is so severe that two tablets do not afford relief, an acute coronary episode may be threatening. If this is suspected, nitroglycerin is contraindicated, and medical advice should be sought.

The patient should also be urged to take nitroglycerin prophylactically prior to indulgence in an activity that precipitates an attack, whether it be leaving the house in the morning, going into the cold from a warm apartment, walking after a heavy meal, or sexual intercourse. Thus, if he suffers chest pain when he leaves home in the morning to walk to the garage, subway or bus, climbs stairs, or steps out into the cold air, he should place a tablet of nitroglycerin under his tongue beforehand.

A dose of $\frac{1}{200}$ gr. of nitroglycerin is sufficient for the majority of patients. When even this small amount causes headache or pounding in the head, the dose should be reduced to a $\frac{1}{400}$-gr. tablet.[1] Occasionally, even this amount must be halved. Usually, the dose that does not cause pounding in the head, or headache, is sufficient to relieve chest discomfort. Many times, a dose as large as $\frac{1}{100}$ gr. is necessary and used routinely.

An excess of nitroglycerin in an older person will cause giddiness, fainting sensations, and even syncope. Thus, in treating the elderly, it is especially advisable to prescribe nitroglycerin in small doses, along with an admonition not to take more than two tablets within a few minutes. The explanation for these adverse effects of the drug may lie in the fact that older people have an extremely sensitive carotid sinus.

Dr. Sam Levine of Boston has successfully aborted severe episodes of angina pectoris by lightly massaging the carotid artery. However, in an older person, one should be wary of employing this procedure.

Increasing numbers of older people use nitroglycerin for many symptoms other than pain, pressure, heaviness, and similar sensations in the chest and arms and between the shoulder blades. "Not feeling right," giddiness, faintness, or palpitation of the heart, can be mistakenly interpreted by the patient as an indication for nitroglycerin. The older patient, like all others, must be warned against this habit. Syncope will often result, tachycardia or palpitation will be aggravated, and hypotension will be induced or increased.

Old people are subject to episodes of syncope. Whether the cause be the bradycardia associated with aging, heart block, aortic stenosis, an arteriosclerotic calcified mitral valve, or the associated carotid sinus sensitivity, syncope in some old people is a serious condition that requires treatment. Small doses of

[1] A $\frac{1}{400}$ gr. tablet (#252) is manufactured by Eli Lilly and Company.

atropine or atropine-like drugs which increase the heart rate may be helpful, as may small doses of *ephedrine* or ephedrine-like preparations which not only accelerate the heart rate but elevate low blood pressure.

Besides nitroglycerin, on occasion a *vasodilator* may be prescribed. Various types may be alternated from time to time because of the beneficial psychic effect this may have. I have tried xanthine and theophylline preparations, vitamin E, anticoagulant drugs, heparin, lipotropic agents, quinidine, and rauwolfia preparations without the slightest benefit except for the placebo effect. Tranquilizers perhaps help to create peace of mind. Probably because human beings want a crutch to lean on, patients often believe that they are benefited by these drugs. The pentaerythritol tetranitrate preparations and the theophylline ethylenediamine (aminophylline) group have their adherents among my patients. Strange as it may seem, the very side-effect that the drug produces, (*e.g.*, gastric disturbance, headache, or cerebral stimulation) leads the patient to think that he is deriving benefit. However, whether or not the patient seems benefited, the underlying coronary disease remains unaltered. The abnormal electrocardiogram remains abnormal, and the findings with the "2-step" exercise electrocardiogram remain positive.

Recently, my colleagues and I reported that *iproniazid* (Marsilid) was helpful in severe angina, particularly in status anginosus. It is to be given with caution because of its side-effects, and its use requires skill. It is not advocated unless such skill and supervision are at hand. Less toxic preparations of *monoamine oxidase inhibitors* are available, primarily as *psychic energizers*. Occasionally, they are helpful in severe angina, and it is to be hoped that some new preparation will be a real success—relieve the angina pectoris, have minimal or no side-effects, and perhaps also obviate the underlying coronary disease. The mechanism of action of these energizers is uncertain. They elevate mood. They increase the pain threshhold, act on the autonomic nervous system, and increase the production of serotonin. The underlying coronary disease, however, remains unchanged. In milder cases of depression in older people, psychic energizers may be used cautiously in very small doses. Similarly, in a tense, excited person, some of the new mild tranquilizers are helpful.

Excessive use of tobacco is injurious in coronary disease. If it is difficult for a patient to stop smoking suddenly, he should be urged to experiment. He is permitted to smoke during alternating weeks, and to discover for himself whether tobacco is harmful to him. If, however, the patient can enjoy three, five, or even seven cigarettes, or one or two small cigars daily, or occasionally a pipe, without precipitation of an attack or aggravation of his condition, he should be permitted to indulge to this extent. Rarely some of my patients over 70 years of age smoke two, three, or four cigars a day with enjoyment although they have hypertension and enlarged hearts. The good effect may be psychologic; these patients derive peace of mind and pleasure from smoking a pipe or cigars.

Many patients ask whether *alcoholic beverages* may be taken. This is almost always permitted in moderation, not because it produces coronary artery dilation but because it may serve to relax a tense person. In excess, alcohol is a

stimulant. It increases the heart rate as well as the work of the heart muscle. Its high caloric content results in weight gain, which is always undesirable in persons who are ill, and particularly so in those with an anginal syndrome.

It has become proverbial that alcohol is helpful in the aged person. There is no doubt that one to three small drinks a day give the older person a boost in morale, and this should by all means be continued. I have never seen a very old patient become a chronic alcoholic.

Weight reduction is essential in the treatment of obese patients with coronary disease. Fortunately or unfortunately, in the very old, one does not find extreme overweight, that is, 20 per cent more than "average" weight. This is because such overweight persons do not survive to old age; the underweight do. Obesity puts a strain on the cardiovascular system. Frequently, however, one does find an old patient who is somewhat overweight and in whom the loss of a few pounds will be of benefit. It is very difficult for old people to lose weight—much more so than for younger people. The metabolic rate is low; they do not burn their food like younger persons; and they are not active physically. Nevertheless, I recently observed recovery from acute coronary occlusion in 2 old men aged 76 and 84. At the time of the acute attack, while completely incapacitated, they voluntarily chose to lose weight, and maintained the reduced weight after recovery.

Even in older patients, *appetite-suppressing preparations* can be used for weight control. With those that possess sympathicomimetic activity, a sedative or tranquilizer is also prescribed.

Weight reduction is essential in sufferers from coronary disease. More patients have benefited from weight reduction alone than have been helped by the many drugs that have enjoyed popular appeal since 1920.

Anticholesteremic agents. Not infrequently, one finds an elderly patient with a serum cholesterol level of 300 to 350 mg. per 100 ml. I have never found levels, as high as 500 or 1000 mg., probably because such people do not survive to old age. In any case, patients with a serum cholesterol level of 300 or 350 mg. should be given a low-fat, low-cholesterol diet. In general, it is dangerous to go to extremes when treating older persons. Lipotropic agents may also be used. Nicotinic acid, however, may cause burning, pricking, and flushing sensations.

Status anginosus. Fortunately, this severe form of angina pectoris—requiring 20 to 60 tablets of nitroglycerin a day—is rare both in the young and old, but especially in the latter. Although patients may live with this disease for many years, it is an extremely serious lesion. A man aged 76, a woman aged 77, and the 2 women aged 80 whom I have mentioned suffered from this malady for five to ten years before they died. For such patients especially, and for others who have frequent attacks of angina pectoris, constantly repeated reassurances and encouragement are essential. The patient must be encouraged to believe that if he cooperates, he will do well. The more frequent the pain, the more often will it return; the less frequent the pain, the less apt is it to recur. Hence, in an attempt to break the vicious cycle of chest pain and apprehension, small doses of *a narcotic*, such as codeine, dihydromorphinone hydrochloride (Dilaudid) or

pentiopium hydrochloride (Pantopon), should be prescribed for two weeks in the hope that the pain will then be wholly relieved or considerably diminished.

Operative treatment of angina pectoris should be considered only when a thorough medical regimen has not proved efficacious.

In patients with status anginosus, every means of relief, even operative, is indicated. This condition requires the most meticulous care and the closest cooperaton between the physician, surgeon, anesthesiologist and the nurses. Many procedures may be undertaken—paravertebral block, sympathectomy of the upper left and right dorsal ganglia, cardio-pericardiopexy, anastomosis of a branch of the aorta into the coronary sinus or myocardium, or double ligations of the internal mammary artery at the second intercostal space. Though the latter is a minor procedure and though the reports are enthusiastic, further evidence of its usefulness should be awaited. A favorite procedure at present is cardio-pericardiopexy with removal of the sympathetic vertebral ganglion from within the thorax at the time of operation.

Radioactive iodine should be given a trial. Although it has helped patients with the ordinary anginal syndrome, it has been of no benefit to 2 of our patients with status anginosus.

Radiotherapy over the heart region has been advocated for severe angina pectoris. The rationale is that new or collateral circulation will be formed. Good evidence has been presented for this effect in experimental work, but it has not yet been proved clinically.

Rarely is it necessary to advise patients to go to *warmer climates* during the winter months. With reassurance and the use of nitroglycerin prophylactically, they suffer no more than in the summer. However, severe cold weather may prove deleterious unless the patient learns to keep warm. Lightweight, warm woolen underwear, socks, vests, sweaters, and overcoats are a great comfort. Warm overcoats weighing only 4 pounds are available. Thin, lightweight woolen underwear also is available, even some with long sleeves and legs.

High altitudes do not aggravate or precipitate angina pectoris, unless the patient exerts himself unduly, or unless the elevation is more than 7,000 feet. Altitudes up to 3,000 feet play no role, and reassurance of the patient on this point gives him confidence.

Physical exertion, within the limits of myocardial reserve, is good for morale and even good for the heart. Walking and swimming are excellent exercises, in moderation. However, a patient with an anginal syndrome or significant coronary disease should be prevented from *shovelling snow*. Such effort in the cold is obviously dangerous, and may precipitate an attack of coronary insufficiency without occlusion but with subendocardial ischemia or necrosis. Shovelling may be excellent exercise for the healthy, but most precarious for a man with coronary disease, particularly if he is aged.

The older person should be encouraged to move about, walk, climb and swim even if it must be done very gently. He should not watch television in a cramped sitting position for any length of time, but should get up every ten or fifteen minutes and move about the room. Sitting in one place tends to promote thrombosis.

The elderly 99-year-old judge, mentioned previously, travels to court every day by subway. He will not use the elevator (by preference), but climbs the many steps leading from the street to the entrance of the courthouse. He climbs the steps slowly and at a slant, which allows more rest between each step.

Legitimate major or minor *operations for extracardiac conditions* are not contraindicated in a patient with significant coronary disease. On the contrary, the removal of foci of irritation, infection and aggravation is indicated. Thus, gallstones causing recurrent attacks of colic should be removed. With the new techniques employed in anesthesiology and surgery, such operations are no longer dangerous in patients who suffer from coronary artery disease.

A patient with coronary disease can react better to a major operation than does a healthy person—unorthodox as this statement at first may seem! Such a result is possible if the cardiologist or practicing physician, the anesthesiologist, and the surgeon work hand in hand. The experienced anesthesiologist should give the anesthetic of his choice. Thus, he should not be enjoined from employing spinal anesthesia if he thinks it is the best method, but the surgeon should insist that the blood pressure not be permitted to drop. The anesthesiologist must preserve an open airway to the lung, see that pulmonary ventilation is adequate, administer sufficient oxygen, and insure the avoidance of pain and fear, as pain or fear may precipitate an episode of acute coronary insufficiency without occlusion. Sedatives and tranquilizing agents are prescribed. The patient must not be permitted to become cyanotic for even an instant. Blood transfusions should be given immediately, if a hemorrhage occurs. Digitalization should be reserved for cases of heart failure; it must not be used routinely in all cardiac patients who undergo operation.

An uneventful postoperative course has been observed in a 92-year-old man with coronary disease who was operated upon for an abdominal neoplasm. In another man, aged 84, with chronic heart failure, complete heart block and Stokes-Adams attacks (a non-cooperative patient to boot) anuria suddenly developed. Relief was obtained in the hospital by using an indwelling catheter, but a prostatectomy became necessary. The patient insisted upon a one-stage procedure, which was performed. He was watched by the cardiologist, the anesthesiologist and the surgeon. Severe hemorrhage from the bed of the prostate occurred during the operation, but transfusions were continued while the urologist tried to find the bleeding point through the cystoscope. The patient was returned to the operating room twice during the next twenty-four hours because of renewed hemorrhage. Despite all of this, he recovered and lived four years.

Although *estrogens*, in theory, should be of value in the treatment of angina pectoris, I have not found them useful.

ACUTE CORONARY INSUFFICIENCY WITHOUT CORONARY OCCLUSION (SUBENDOCARDIAL ISCHEMIA OR NECROSIS)

This condition is actually a severe and prolonged episode of angina pectoris. In the past, the need for such a subdivision of coronary disease was often questioned, for, in a broad sense, all coronary disease is "coronary insufficiency"; angina pectoris can be considered as the mild form, and coronary occlusion as

the complete form. However, the stage without occlusion, intermediate between "angina" and "occlusion," should be accepted for practical reasons. Coronary insufficiency without occlusion often can be prevented and cured, whereas acute coronary occlusion can neither be foreseen nor prevented. Moreover, the latter can be treated only symptomatically, once it has occurred, and it occurs spontaneously without a precipitating factor.

Coronary insufficiency without occlusion (*i.e.*, without complete transmural infarction) may be induced by conditions that 1) increase the work of the heart, 2) diminish the coronary flow, or 3) interfere with oxygenation of the blood, or 4) by a combination of these. The majority of attacks, however, are spontaneous, pursue a mild course, and have a good to excellent prognosis.

When acute coronary insufficiency without occlusion is precipitated by *increased work of the heart* (*e.g.*, strenuous physical work or paroxysmal tachycardia) these factors must be eliminated. Physical activities should be curtailed, and straining at stool avoided. Nitroglycerin should be employed without hesitancy before the anticipated exertion, in order to prevent chest or arm discomfort. Paroxysmal tachycardia should be treated with digitalis, quinidine and vasopressor drugs. For thyrotoxicosis, the administration of radioactive iodine or propylthiouracil may be necessary, or surgery may be undertaken. For acute infections, antibiotics should be given.

Although the older patient with coronary artery disease should walk, climb, play golf and even swim, (gently and in moderation), such activities as shovelling snow or riding a bicycle uphill are contraindicated. Shovelling snow is dangerous because the cold and the physical effort put an inordinate strain on the heart. Although this form of exercise may not cause acute coronary occlusion with transmural infarction, it can, in patients with significant coronary artery disease, produce acute coronary insufficiency without occlusion but with subendocardial infarction. Occasionally, it may cause death.

Acute coronary insufficiency without occlusion due to *diminished coronary flow* often occurs as a result of shock or hemorrhage. Prompt recognition and treatment of the causative condition are essential for recovery. For *shock*, prompt treatment should be directed toward increasing the blood volume, the blood pressure, and the hemoglobin concentration to normal levels. We employ the sympathomimetic and the vasopressor drugs, *e.g.*, phenylephrine (Neosynephrine), norepinephrine (Levophed), methoxamine (Vaxoxyl), and mephentermine (Wyamine). For *hemorrhage*, repeated transfusions may be necessary. Fluid and plasma may be administered, but whole blood is best. In the past, surgeons argued with internists as to the relative merits of medical and surgical treatment of bleeding ulcer. Often, while this debate proceeded, the patient died—not from exsanguination, but from subendocardial infarction due to acute coronary insufficiency without occlusion. Now, such patients survive. Frequently repeated transfusions in cases of gastric or rectal bleeding (for example, ulcerative colitis) work wonders. Death from these conditions is now relatively rare. For the prevention and treatment of hypotension during spinal anesthesia, administration of ephedrine, paredrine, or phenylephrine is effective.

If heart failure is present, digitalis also is prescribed as well as mercurial diuretics, thiazide derivatives and a salt-restricted diet.

Acute coronary insufficiency without occlusion may be produced by *diminished oxygenation* of the blood *e.g.*, during anesthesia, during operation, or in patients suffering from anemia or pulmonary insufficiency. Pulmonary insufficiency, including status asthmaticus, is now treated with oxygen under pressure, theophylline ethylendiamine (aminophylline), epinephrine, chemotherapy, and the aerosols with a host of mechanical aids. The common belief that death is due to pulmonary embolism and infarction because of right heart failure is probably wrong. Death usually is due to acute coronary insufficiency without occlusion, but with subendocardial ischemia or necrosis. An attempt should be made to prevent pulmonary embolism by early postoperative ambulation, and by the administration of heparin and other anticoagulants.

Although three chief possible causes of coronary insufficiency without occlusion have been discussed, the condition is likely to be the result of a combination of these factors rather than a single factor. Many attacks of coronary insufficiency without occlusion appear to be spontaneous; nevertheless, a precipitating factor can be identified in thousands of cases daily. Thus, morbidity and death can be prevented by the procedures outlined.

ACUTE CORONARY OCCLUSION

Acute coronary occlusion signifies a complete closure of a coronary artery with usually complete transmural infarction extending from the endocardium through the myocardium and involving the pericardium.

The impression is that very old people rarely suffer from coronary occlusion. This is still an open question, and the impression may be based upon the fact that there are many fewer old people than there are people between 40 and 60 years of age. Coronary occlusion is associated with severe coronary sclerosis, and therefore the patient likely will not live to a ripe old age. However, among patients who cooperate, we are going to find more and more of them living into their 90's. No matter what the age, acute coronary occlusion will occur. So-called "silent" attacks are probably more frequent in the aged.

Most cases of coronary occlusion can be treated at home rather than in the hospital, even if anticoagulants, oxygen, and vasopressor drugs for shock must be administered.

Morphine and morphine derivatives, such as dihydromorphinone (Dilaudid) and opium alkaloids (Pantopon), are most efficacious for the relief of severe pain, whereas meperidine (Demerol) is not. However, narcotics should be given only when necessary. Oxygen should be administered to prevent respiratory depression; it also may help to relieve the pain, as may a suppository of theophylline ethylenediamine.

It must be constantly stressed that older people do not tolerate large doses of drugs as well as middle-aged and young adults do. Small doses must be prescribed and side-effects must be watched for closely. Thus, even if small doses of narcotics are given, the constipating effect must be counteracted. Laxatives,

cathartics, low enemas of soapy water or phosphate of soda should be given. The patient should not be permitted to go without a bowel movement for more than two days. Above all, the elderly patient must never strain to move his bowels. If he strains at stool, he is liable to add acute coronary insufficiency to the occlusion and endanger his life.

The older patient with an acute coronary occlusion may have difficulty passing urine if he is taking a narcotic; therefore, he should be helped to stand beside the bed when using the urinal. Because of this inhibiting effect, it is all the more advisable to give a minimal dose of narcotic.

Fatigue is not uncommon in the older patient and one must be sure that no anemia or other disease is present to cause the "weakness." *Caffeine* (½ to 1 grain) may be given in the morning and at noontime; it is more effective than black coffee. If given late in the afternoon, it may keep the patient awake. Coca-Cola or Pepsi Cola may have the same effect as caffeine, but they are less desirable as they may cause a gain in weight.

Vasopressor drugs (tablet form) help to overcome fatigue, especially when hypotension is present. For example, in a man aged 80, fatigue is associated with low blood pressure. When he is not taking mephentermine he cannot function. He is "terribly tired," and upon moving his head or body, may faint. Without this therapy, he has hypotension (blood pressure, 90 to 96 mm. Hg), but when taking a 15-mg. tablet of mephentermine twice a day, he leads a useful life.

The value of *anticoagulant drugs* for all cases of coronary thrombosis is no longer undecided. Since the President's illness and the publicity engendered by it, patients and their families expect and insist on their use. Because of this popular desire, the physician is constrained to give an anticoagulant to every patient with coronary disease. Otherwise, if an occlusion occurs, even years later, the family of the patient will think that, had anticoagulant therapy been used, the coronary accident might have been prevented. Anticoagulant drugs, without question, are indicated in the seriously sick, in patients with congestive failure or in a state of shock, in those with a history or evidence of embolism, thrombosis or phlebitis, and in obese or debilitated patients whose movements are restricted or who are confined to bed for long periods. Anticoagulants are definitely contraindicated in patients with a history of hepatic, gastric, or renal disease, in patients with a hemorrhagic tendency, and in those with ulcerative colitis.

No single anticoagulant is especially effective in comparison with another. It is, therefore, wise for the physician to use that drug with which he is best acquainted. More important is the fact that the administration of anticoagulants requires careful supervision. The patient and nurse should be advised to inspect the stool, in order to be sure that it is not tarry. It is also advisable to have a test-tube specimen of the last urine always available for inspection. If the urine becomes rust colored, it is a warning of an increase in prothrombin time and possible gross hemorrhage. If hemorrhage does occur during treatment with heparin, protamine sulfate intravenously and transfusions should be given. If Dicumarol or a coumadin derivative is employed, intravenous vitamin K_1 and transfusions should be used to counteract the effect of the anticoagulant.

Anticoagulants should be tapered off gradually. If stopped abruptly, the result may be a rebound hypercoagulability.

It is doubtful whether anticoagulants given during the "premonitory phase" of coronary occlusion have any effect on its development, though many believe that they have. My colleagues and I are gathering information on this point.

It was once believed that anticoagulants are contraindicated in old age. This is not the case. Nevertheless, older patients do require more supervision, and they should become ambulatory at the first possible moment consistent with safety.

Early ambulation. It has been thought that anticoagulants are unnecessary in mild cases of coronary occlusion. This controversial point is not as important as it appears, since patients do not remain in bed longer than is necessary, and the milder the lesion the earlier the ambulation. Patients should gradually begin to walk during the second, third and fourth weeks of their illness. English physicians, as well as William Dock, Tinsley Harrison and Sam Levine in America, insist upon getting the patients sitting up in a chair as early as possible. Since many patients consider the bedpan to be an invention of the devil, they should be allowed, if possible, to use a commode or permitted to go to the toilet on the second or third day of their illness. This mild activity boosts morale, helps to overcome peripheral blood stasis and the tendency to thrombus formation, and prevents constipation and distention. If the patient must remain in bed, he should be urged to change his position gently, wiggle his toes, and move his feet frequently but gingerly. Some physicians recommend that the feet and legs be bound with "Ace" bandages.

It is neither necessary nor wise to enforce a six-week bed rest, as in the past, nor to feed the patient three times a day. Until a few years ago, some institutions were still carrying out such a program in spite of the shortage of beds and nurses. At present, walking is permitted during the fourth or possibly the third week following the occlusion. The patient is then sent home. This makes scarce hospital beds available, saves nursing, and is more economical for the patient. However, these procedures apply only to the mild or moderately severe case of coronary occlusion with good recovery. The severely sick patient may require months in chair and bed.

A "*morale talk*" should be given to the patient as soon as advisable. Any person who has led an active life feels greatly depressed during the early stages of coronary occlusion. He believes that his physical, financial, emotional and sexual life has come to an end. He, therefore, must be encouraged and assured that he will return to normal activities.

The older person has just as strong a desire to live as does the younger person; it cannot be taken for granted that he has attained the wisdom and equanimity of a Solomon and is prepared to meet The Maker. Nor can it be assumed that the relatives have lost interest in the old patient. It may be a mistake to conclude that because the sons and daughters have had their parents for so many years they would be thankful for this and not take death too hard. On the contrary, the attachment may be all the deeper for being prolonged.

Prevention of infections. Penicillin (600,000 units) should be given in the first

three days after acute coronary occlusion. This small dose given for only three days is not liable to elicit a sensitivity reaction. It is my impression that the antibiotic has prevented complications due to infection.

The patient may have a habit of lifting himself higher in bed using his arms as levers. This *stress* is dangerous. He must be admonished to ring for help when he desires elevation of the head of the bed or wishes to be pushed up on the pillows.

Years ago, a patient with coronary occlusion was given a high calorie (3000 to 5000) carbohydrate liquid diet. This increased the work load of an already weakened heart muscle. Today, a *low calorie diet* is prescribed, particularly during the first week, and as long as necessary thereafter for an overweight person. This prevents gastrocardiac reflexes, decreases the work of the heart, and results in weight reduction.

Distention and constipation are serious complications of acute coronary occlusion. After forty-eight hours, if the patient has not had a bowel movement, a *laxative* should be prescribed. The patient must be reminded constantly not to strain at stool during his acute illness or thereafter.

Nausea and vomiting are serious complications of coronary occlusion, and may be caused by drug therapy (*e.g.*, digitalis, ammonium chloride, quinidine, theophylline ethylenediamine and a host of other preparations). In treating nausea and vomiting, the diet should be kept very light; fruit juices, raw milk, and fried and spicy foods should be avoided. Cracked ice may be sucked. If the symptoms do not abate, drugs for motion sickness—dimenhydrinate (Dramamine), cyclizine (Marezine), or meclizine hydrochloride (Bonadoxin)—may be given by mouth. Although chlorpromazine (Thorazine) and derivatives like prochlorperazine (Compazine) are perhaps the best drugs for the relief of nausea and vomiting, they have a tendency to lower blood pressure. Therefore, they are dangerous in acute coronary occlusion.

Digitalis should be employed in cases of *heart failure*. The failure should be treated vigorously, but it is essential to avoid digitalis intoxication, which may be especially serious because of the already damaged myocardium. The optimal dosage of digitalis varies with each patient. Nausea, vomiting and diarrhea are late manifestations of digitalis intoxication. The patient should be told to watch for the appearance of signs of cerebral excitation or depression, visual disturbances, sudden nausea and loss of strength or appetite, and later, vomiting and diarrhea. If intoxication does occur, potassium, atropine, and fruit juices are antidotes. Theophylline ethylenediamine (aminophylline) has been used successfully, as has chlorpromazine. Chelating agents, such as ethylenediamine tetra-acetic acid, are of value because they bind serum calcium.

Digitalis is as helpful in the older as in the younger person, but extremely low dosages may be necessary We have observed 2 patients with heart failure, 76 and 84 years of age respectively, who required as little as 2 half-units of digitalis leaf a week (or the equivalent of other digitalis preparations). The vagus is particularly sensitive in older people, and digitalization may result in bradycardia sufficient to produce dizzy spells. Partial or complete heart block may be

precipitated, particularly in a patient whose electrocardiogram already shows a prolonged P-R interval.

A *low-salt diet* should never be too strict. Even in severe heart failure, the patient preferably should take ½ or 1 gram of salt a day.

Electrolyte balance is extremely important. Daily injections of a mercurial diuretic may lead to a low-sodium syndrome or to such pronounced dehydration as to encourage thrombosis. Patients can die of cerebral thrombosis following a severe "drying out" by mercurial diuretics. The levels of serum sodium, potassium, chlorides, CO_2 combining power, and proteins should be watched carefully.

Diuretics. Chlorothiazide and hydrochlorothiazide have lived up to their promise and have proved effective in the treatment of heart failure. The still newer thiazide preparations such as hydroflumethiazide (Saluron), benzhydroflumethiazide (Naturetin) or trichlormethiazide (Naqua) have also proved helpful when digitalis and injections of a mercurial diuretic or acetazolamide (Diamox), ammonium chloride, restriction of salt, and the other time-honored methods have been of no avail. Since potassium excretion is promoted by the thiazides, citrus fruit juices and potassium preparations, or both should be given. The appearance of premature beats should serve as an immediate indication for the administration of potassium.

The *spirolactones* may play an important role in the treatment of heart failure. These steroids occasionally break up severe or intractable heart failure, particularly that associated with the post-myocardial syndrome.

Whiskey should not be prescribed during the acute phase of coronary occlusion. We know of 2 patients who possibly died as a result of its use—one was ordered to take an ounce every second hour, and the other an ounce every hour!

Experimentally, *cortisone* and its newer derivatives and *corticotropin* (*ACTH*) decrease the size of the infarct produced by coronary artery ligation. Thus far, however, these drugs have not been successful clinically except in occasional refractory failure. They may be dangerous in acute coronary occlusion.

Pulmonary edema should be treated energetically with morphine, aminophylline, a mercurial diuretic, oxygen, oxygen under pressure, strophanthin, digitalis, rotating tourniquets, and other techniques.

Shock in coronary thrombosis should be combatted immediately. Many preparations may be used, among them phenylephrine (Neosynephrine), norepinephrine (Levophed), metaraminal (Aramine), mephentermine (Wyamine), and and methoxamine (Vasoxyl). These may be life-saving, when given very early. In fact, one should not wait for evidence of clinical shock; if the blood pressure drops to 90–60 mm. Hg, these drugs should be administered immediately.

If norepinephrine is used, the tissue around the site of injection may become necrotic. This should be treated by injecting phentolamine (Regitine), tolazoline hydrochloride (Priscoline), and hyaluronidase into the area involved.

Intractable hiccough is now rarely seen as a complication of acute coronary occlusion, but is most serious if it does occur. The physician should not appear panicky, but maintain an attitude of assurance and nonchalance in order not to alarm the patient further. Many drugs and maneuvers have been used to over-

come hiccough. Sedation, the use of a paper rebreathing bag, "carbogen tanks," quinidine intramuscularly, niacin, atropine intravenously, amyl nitrite, ethyl chloride sprayed on the skin along the border of the diaphragm, ether as an anesthetic or by subcutaneous injection, stellate ganglion block, phrenicectomy, execresis of the phrenic nerve, and stomach lavage have each proved efficacious in individual cases. If chlorpromazine is used, it must be given only in small doses in cases of coronary occlusion, and the patient watched assiduously because of the tendency of this drug and its popular derivatives to produce dangerous hypotension.

In *nonspecific pericarditis*, anticoagulant therapy is dangerous, since hemopericardium may occur. Because nonspecific pericarditis is often mistaken for coronary occlusion, the differential diagnosis must be established clinically and electrocardiographically. No Q-waves appear in the electrocardiogram of nonspecific pericarditis. Moreover, when other means of therapy fail to relieve pain or the disease becomes protracted, steroids may produce a "miraculous" cure in nonspecific pericarditis, whereas they are ineffective in acute coronary occlusion.

The post-myocardial syndrome following acute coronary occlusion was recently described and its frequency emphasized by Dressler. It is difficult to gauge how common it is in old people. However, we have seen it in a man aged 65. It may be a serious prolonged complication of coronary occlusion with "intractable heart failure." Steroids have proved highly successful in treating protracted cases of this syndrome. Probably this entity and the post-commissurotomy syndrome following operations on patients with valvular heart disease are caused by a virus infection. Perhaps nonspecific pericarditis is also in this category, as an acute respiratory infection often precedes it. In our cases of the post-myocardial syndrome any upper respiratory infections occurred in patients in whom antibiotics had not been given during the first three days of illness.

Changes toward normal in the *electrocardiogram* during the first year or so following acute coronary occlusion are a good prognostic omen, but the contrary is not true. The patient may have made an excellent recovery, whereas his electrocardiogram may still show deep Q-waves, RS-T segment deviations, and T-wave inversions. In fact, clinical progress may be satisfactory despite an enlarged heart and a ventricular aneurysm causing electrocardiographic Q-waves and persistent RS-T segment elevations.

In general, *abnormal electrocardiograms* in the elderly signify much less than they do in the middle-aged. Thus deeply inverted T-waves, left bundle-branch block patterns, intraventricular block, deep Q-waves with RS-T segment elevations (*e.g.*, in ventricular aneurysm), or RS-T depressions are repeatedly observed in patients with complete absence or paucity of symptoms. An anginal syndrome that was only mild to moderate may disappear and yet the electrocardiographic abnormalities may persist and occasionally grow worse. Undoubtedly, collateral circulation has come into use. Then, too, the patient often learns to live with his coronary disease, leads a sensible life, avoids physical stress and mental and emotional crises, and carries no excess weight.

In older people with coronary disease, the *erythrocyte sedimentation rate* often remains elevated at 30–60 mm. per hour in the absence of any acute manifestation of illness. The patient may be active and working, and have no complaints. A nationally and internationally famous surgeon, 80 years of age, had two attacks of acute coronary occlusion, fifteen and five years ago, is still active and performs operations. Yet for three years after his first coronary occlusion he was extremely worried in spite of continued reassurance, because his sedimentation rate was always reported as between 35 and 60 mm. per hour.

In the past, physicians were afraid to advise their patients to *return to work*. Rather, the patients were to remain invalids—an attitude which the old-type liberal disability insurance allowance frequently fostered and abetted. Now, however, one can inject a note of optimism. Although the incidence of coronary occlusion is high, the mortality rate is probably less than 20 per cent for patients in hospitals. In the third decade of this century, the mortality from coronary occlusion was 40 to 60 per cent in the best institutions! In private practice, the mortality rate for first attacks of coronary occlusion is now 5 per cent or slightly less. Patients can now be *rehabilitated*. It is good for their morale; they are willing and even anxious to resume full-time or part-time jobs.

Outlook. That coronary occlusion is an extremely serious disease is unquestioned. However, improved diagnostic techniques for ready recognition of the attack, a better understanding of the disease by both physicians and the laity, and a more rational form of treatment have all had a share in the remarkably improved outlook.

Continued study and research will improve still further the immediate and long-term prognosis of patients who suffer from coronary occlusion. Perhaps therapeutic advances will involve an enzyme that will prevent or dissolve thrombi, a lipotropic agent that will prevent the formation of cholesterol plaques in the intima of the coronary arteries, some operation such as "reaming out of the diseased coronary arteries," or a new form of radiotherapy. What seems fantastic and even ludicrous now may not appear so in a short while. The remarkable strides being made in biochemical research, and the daring operations performed even on individual coronary arteries, justify great optimism for the future. The not unreasonable hope is that arteriosclerosis, which is apparently a disease and not an "inevitable result of aging," may some day be prevented, and that the present common disease of coronary thrombosis will become rare clinical entity.

SUMMARY

Acute coronary artery disease is manifested clinically in three distinct forms: 1) angina pectoris, 2) coronary insufficiency without occlusion, and 3) coronary occlusion. As applied to the elderly patient, the treatment of each is presented in detail and the prognosis is discussed.

URINARY ESTROGEN AND GONADOTROPIN EXCRETION IN ELDERLY WOMEN AND THE PLASMA CORTICOID RESPONSE TO CORTICOTROPIN*

ROBERT L. NIELSEN, M.D.,† DONALD MOORE, B.S. AND C. ALVIN PAULSEN, M.D.‡

The Mason Clinic and The Pacific Northwest Research Foundation, Seattle, Washington

In old age, clinical changes appear which in a younger group would suggest endocrine hypofunction. These changes include depigmentation, decrease or loss of axillary and pubic hair, thin wrinkled dry skin, thin eyebrows, loss of muscular strength and loss of general vigor. Studies of endocrine function in elderly patients (1, 2) tend to show dissociative changes in function not only between different glands but also different functions of the same gland. Androgen production, as measured by urinary 17-ketosteroid excretion in both sexes, is uniformly reduced with advancing age (3), yet the ability of the adrenal to produce glucocorticoids seems little if at all impaired and there is no evidence of a corresponding decrease in aldosterone production. In the female, estrogen levels uniformly diminish and gonadotropin levels rise. There is controversy, however, about whether gonadotropin excretion stays elevated or whether it shows a slow decline with advancing years (4, 5).

Thyroid function usually changes little if at all. Not much is known regarding the effect of age on corticotropin (ACTH) production. The secretion of pituitary growth hormone may increase slightly in postmenopausal women, with removal of estrogen suppression (6).

The present study was undertaken in an effort to delineate adrenal and ovarian function in a group of old women.

CLINICAL MATERIAL AND METHODS

Eighteen women were studied. They ranged in age from 76 to 91, with median age of 82. All were postmenopausal and none had undergone pelvic surgery or pelvic irradiation. None bore evidence of carcinoma of the breast or of any other malignant condition. They were studied in the convalescent unit of the King County Hospital in Seattle, where they were convalescing from various types of trauma, mostly fracture of the femoral neck. In all cases, more than a month had transpired after the injury or after any surgical procedure. No patient was bedridden, and all were receiving active daily physiotherapy. Only one had been treated with hormones, and she had received none for over two years prior to the study. No patient was clinically edematous, and none manifested any evidence of overt complicating disease, although several were receiving digitalis for well-compensated heart disease. All patients were free of overt urinary-tract infection, uremia and acidosis, and none had been taking medications which might interfere with the hormonal determinations. All were mentally competent.

Adrenal function was assessed by measuring the plasma level of Porter-Silber chromo-

* Presented at the 17th Annual Meeting of the American Geriatrics Society, Americana Hotel, Miami Beach, Florida, June 9 and 10, 1960.

† Clinical Instructor of Medicine, University of Washington.

‡ Clinical Assistant Professor of Medicine, University of Washington.

gens (corticosteroids) by the method of Peterson *et al.* (7), before and after the intravenous administration of 25 units of ACTH in 500 ml. of dextrose in water over a four-hour period. All of the infusions were given in the morning from 8:00 a.m. until noon.

Gonadal function was assessed by measuring the 24-hour excretion of estrogen (8). Urines were collected without preservative in iced containers. Estrogen was assayed biologically in immature female rats. The uterine weight response to the phenolic fraction of urine subjected to acid hydrolysis and chloroform extraction was compared with the response to a known standard, estradiol benzoate. The results are, therefore, expressed as microgram-equivalents of estradiol benzoate per twenty-four hours.

Gonadotropins in urine were concentrated by the kaolin-acetone method, using a "speed filter." The ovarian weight response in immature rats served as the assay method (9). The results are expressed in terms of the standard preparation, HMG-J-5 (10).

RESULTS

Plasma corticosteroids

The control levels of plasma corticosteroids ranged from 9.5 to 40.8 μg. per 100 ml., with a mean of 18.6 μg. (Table 1). These values are well within the range of normal and are strikingly similar to those reported by Samuels *et al.* (11) for old subjects.

The plasma corticoid response to ACTH, in the majority of patients, was also within the normal range (12) (Fig. 1). In none of the patients was the response subnormal, but in 4 there was "hyper-responsiveness" of the degree usually seen in Cushing's syndrome with adrenal hyperplasia (13). Clinically

TABLE 1

Hormonal Data on 18 Elderly Women

Age of patient (yrs.)	Osteoporosis	Plasma corticoids (μg./100 ml.)		Urinary	
		Control	After ACTH	Gonadotropins (mg.-equiv. HMG-J-5/24 hrs.)	Estrogens (μg.-equiv. estradiol/24 hrs.)
86	+	15.5	47.1	0.66	<0.2
88	−	16.4	39.8	1.10	0.4
82	−	24.7	62.8	0.45	0.5
81	−	13.9	47.2	2.8	<0.2
82	−	13.7	45.0	2.99	0.3
84	−	15.0	37.7	0.38	0.6
78	−	17.9	54.0	1.87	1.4
83	+	23.5	60.8	7.3	<0.2
91	+	9.5	32.7	1.3	<0.2
80	−	16.3	45.0	1.4	0.3
81	−	19.0	50.6	4.1	0.4
76	−	15.8	40.4	2.7	0.3
82	+	17.7	40.7	1.5	—
76	−	40.8	59.1	2.2	0.3
80	−	23.8	56.8	2.2	0.3
75	+	18.9	48.6	1.1	<0.2
81	+	22.0	50.0	1.1	<0.2
83	−	11.2	46.3	—	—

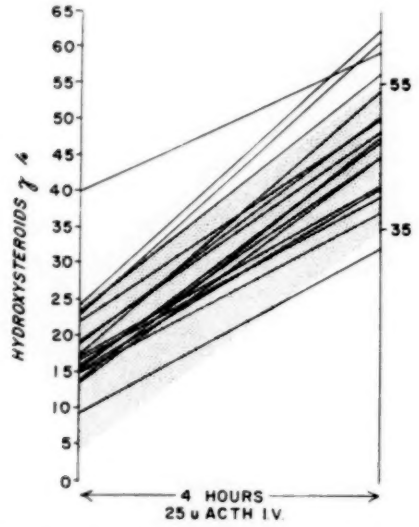

FIG. 1. Plasma corticoid response to infusion of ACTH.

there was nothing to suggest Cushing's syndrome in these 4 women, nor did they differ in any discernible way from the other 14 patients. Thus, in the total group, the plasma corticoid response to ACTH stimulation was not depressed. Whether or not one can assume that adrenal functional capacity was adequate is another matter.

Data presented by Samuels *et al.* (11, 13) showed a prolonged half-life of steroids in elderly patients and a decrease in the distribution volume of corticoids in old age. Their data suggest a rather abrupt change in this respect between the ages of 55 and 65. If age *per se* accounts for this change, however, one would expect to find a progressive change with aging. This was not apparent in our small group; there was no correlation between age and either the control plasma corticoid level or the corticoid response to ACTH (Fig. 2). The plasma corticoid concentration was also not correlated with estrogen excretion (Table 1). Administration of estrogen induces a rise in the level of plasma corticoids, presumably due to an increase in protein binding, but the converse does not seem to be true (14). Thus, even in those patients with no measurable urinary estrogen, the concentration of plasma corticoids was not low, nor was there any significant difference in the response to ACTH between these patients and those with somewhat higher values for urinary estrogen. The lack of correlation between urinary estrogen and plasma corticoid levels would add weight to the hypothesis that most of the estrogen in the postmenopausal woman comes from the ovary and not from the adrenal (4).

Urinary estrogen excretion

As would be expected in postmenopausal women, urinary estrogen excretion was low in the 16 women in whom it was measured. In fact, in 6 of the 16, no estrogenic substance could be detected by the method used (Fig. 3). The mean

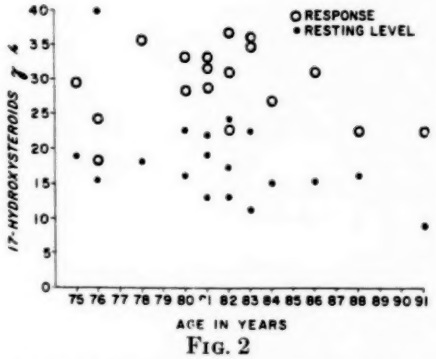

FIG. 2

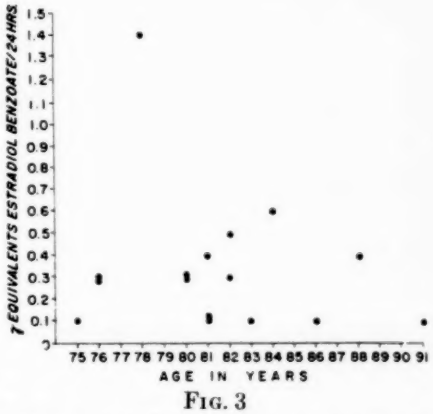

FIG. 3

FIG. 2. Lack of correlation between age of patient and either the control (resting) plasma corticoid level or the corticoid response to infusion of ACTH.

FIG. 3. Urinary estrogen excretion related to advancing age. In 6 of the 16 subjects in whom estrogen excretion was studied the values were below 0.2 μg.-equivalent (*i.e.*, undetectable by the method used). For statistical calculation, values of less than 0.2 μg. were arbitrarily assigned a value of 0.1 μg.

level was 0.26 ± 0.05 (S.E.) microgram-equivalents of estradiol benzoate per twenty-four hours. This value is lower than that previously reported (4) for a group of younger postmenopausal women with a median age of 58 years (0.35 ± 0.04 μg.-equivalents). Although this difference is not statistically significant, the incidence of negative estrogen titers in the younger group was 25 per cent, compared with 37 per cent in the older group. In 45 per cent of surgically castrated women, there is no detectable excretion of estrogen (4). Thus, in the present group of old women, estrogen excretion was midway between the levels found in castrated women and in younger postmenopausal women, despite the fact that no correlation was observed between estrogen excretion and chronologic age in this study. The data suggest a continued decline in estrogen production with advancing years. Alternatively, the presence of osteoporosis in the present group may account for the lowered estrogen excretion.

Postmenopausal osteoporosis is presumably related to estrogen deficiency in the postmenopausal woman (15). The concept that lack of estrogen is the only, or even the primary etiologic factor in the development of osteoporosis has been vigorously attacked. The studies of Anderson (16), Nordin (17) and Whedon (18) implicate a longstanding calcium deficiency as the etiologic factor. It is difficult to understand, however, how calcium deficiency would lead to osteoporosis and not to osteomalacia. Studies of a small group of patients by Urist (19), measuring estrogens by Brown's method (20), failed to show any correlation between osteoporosis and urinary estrogen levels.

Osteoporosis was present in 5 of our 18 patients. We have arbitrarily chosen to define osteoporosis as the presence of vertebral deformity—either severe "cod-fishing" or collapse. Osteoporosis must be present for some time before these changes occur, but an accurate radiologic diagnosis cannot be made in the absence of these deforming alterations (15).

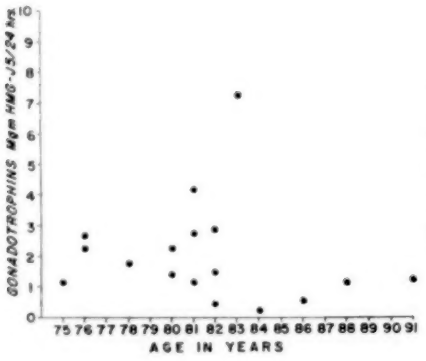

FIG. 4

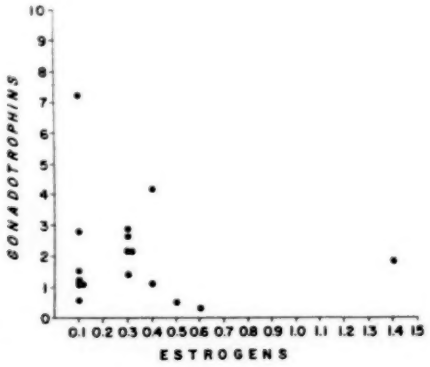

FIG. 5

FIG. 4. Excretion of gonadotropins in old women.
FIG. 5. Lack of inverse correlation between urinary estrogens and gonadotropins.

In none of the 5 patients with vertebral collapse were we able to detect any urinary estrogen. Although this is a very small group and these findings are not statistically significant, they indicate a correlation between lack of estrogen and osteoporosis. There was no correlation between osteoporosis and either the plasma corticoid level or the corticoid response to ACTH (Table 1). Only 1 of the 4 patients who were "hyper-responsive" to ACTH had osteoporosis, and these findings make it seem more likely that it was lack of estrogen *per se* rather than an increase in adrenal function that accounted for its development.

Urinary gonadotropin excretion

Urinary gonadotropins varied from 0.45 to 7.3 mg.-equivalents of HMG-J-5 per twenty-four hours. In all but 3 patients, gonadotropin excretion was elevated. Since a nonspecific reduction in urinary gonadotropin occurs in chronic illness and in conditions of negative nitrogen balance, it is difficult to evaluate pituitary function entirely by this method. Our data (Fig. 4) provided no evidence that aging alone causes a consistent lowering of gonadotropin excretion. Of interest was the lack of inverse correlation between estrogen excretion and gonadotropin excretion (Fig. 5).

SUMMARY

A study is presented of the endocrine status of 18 elderly women aged 76 to 91. It was demonstrated that: 1) adrenal function, as measured by the level of plasma corticoids, was normal, and there was no diminution in the adrenal response to a four-hour infusion of ACTH; 2) urinary estrogen excretion was uniformly low, perhaps even lower than in younger postmenopausal women; 3) there was good correlation between the lack of urinary estrogen and the roentgenologic signs of osteoporosis; and 4) gonadotropin excretion was low in all but 3 patients, but it was so variable that no conclusions could be drawn as to whether gonadotropin excretion declines in extreme old age.

Acknowledgment

The authors wish to thank Dr. K. K. Sherwood and Dr. Philip Peterson for their help and cooperation in studying their patients in the King County Hospital System.

REFERENCES

1. Pincus, G.; Romanoff, L. P., and Carlo, J.: The excretion of urinary steroids by men and women of various ages, *J. Gerontol.* **9:** 113, 1954.
2. Pincus, G.; Dorfman, R. I.; Romanoff, L. P.; Rubin, B.; Bloch, E.; Carlo, J., and Freeman, H.: Steroid metabolism in aging men and women, *Recent Progr. Hormone Res.* **11:** 307, 1955.
3. Hamburger, C.: Normal urinary excretion of neutral 17-ketosteroids with special reference to age and sex variations, *Acta endocrinol.* **1:** 19, 1948.
4. Paulsen, C. A.; Leach, R. B.; Sandberg, H.; Sheinfeld, S., and Maddock, W. O.: Function of the postmenopausal ovary, *J. Am. Geriatrics Soc.* **6:** 803, 1958.
5. Albert, A.; Randall, R. V.; Smith, R. A., and Johnson, C. E.: Urinary excretion of gonadotropin as a function of age, *in* Hormones and the Aging Process, ed. by E. T. Engle and G. Pincus. New York, Academic Press Inc., 1956.
6. Reifenstein, E. C., Jr.; Kinsell, L. W., and Albright, F.: Observations on the use of the serum phosphorus level as an index of pituitary growth hormone activity; the effect of estrogen therapy in acromegaly, (abstract) *Endocrinology* **39:** 71, 1946.
7. Peterson, R. E.; Wyngaarden, J. B.; Guerra, S. L.; Brodie, B. B., and Bunim, J. J.: The physiological disposition and metabolic fate of hydrocortisone in man, *J. Clin. Invest.* **34:** 1779, 1955.
8. Maddock, W. O., and Nelson, W. O.: The effects of chorionic gonadotropin in adult men, *J. Clin. Endocrinol. & Metab.* **12:** 985, 1952.
9. Albert, A.: Human urinary gonadotropin, *Recent Progr. Hormone Res.* **12:** 227, 1956.
10. Albert, A., and Derner, I.: Studies on the biologic characterization of human gonadotropins. IV. Comparison with two new preparations of HPG from the urine of postmenopausal women, *J. Clin. Endocrinol. & Metab.* **20:** 858, 1960.
11. Samuels, L. T.; Brown, H.; Eik-Nes, K.; Tyler, F. H., and Dominguez, O. V.: Extra-adrenal factors affecting the levels of 17-hydroxycorticosteroids in plasma, *in* Hormones in Blood. Volume XI of Ciba Foundation Colloquia on Endocrinology, ed. by G. E. W. Wolstenholme and E. C. P. Millar. Boston, Mass., Little, Brown & Company, 1957, p. 208.
12. Christy, N. P.; Wallace, E. Z., and Jailer, J. W.: The effect of intravenously-administered ACTH on plasma 17,21-dihydroxy-20-ketosteroids in normal individuals and in patients with disorders of the adrenal cortex, *J. Clin. Invest.* **34:** 899, 1955.
13. Samuels, L. T.: Effect of aging on the steroid metabolism as reflected in plasma levels, *in* Hormones and the Aging Process, ed. by E. T. Engle and G. Pincus. New York, Academic Press Inc., 1956.
14. Peterson, R. E.; Nokes, G.; Chen, P. S., Jr., and Black, R. L.: Estrogens and adrenocortical function in man, *J. Clin. Endocrinol. & Metab.* **20:** 495, 1960.
15. Moldawer, M.: Senile osteoporosis; physiological basis of treatment, *A.M.A. Arch. Int. Med.* **96:** 202, 1955.
16. Anderson, I. A.: Postmenopausal osteoporosis; clinical manifestations, and treatment with oestrogens, *Quart. J. Med.* **19:** 67, 1950.
17. Nordin, B. E.: Investigation of bone metabolism with 47Ca, *Proc. Roy. Soc. Med.* **52:** 351, 1959.
18. Whedon, G. D.: Effects of high calcium intake on bones, blood and soft tissues; relationship of calcium intake to balance in osteoporosis, *Fed. Proc.* **18:** 1112, 1959.
19. Urist, M. R.: The problem of osteoporosis, *Clin. Res.* **7:** 377, 1958.
20. Brown, J. B.: Chemical method for determination of oestriol, oestrone and oestradiol in human urine, *Biochem. J.* **60:** 185, 1955.

ORAL AND INTRAVENOUS ESTROGENS IN THE TREATMENT AND PREVENTION OF BLEEDING ASSOCIATED WITH LONG-TERM ANTICOAGULANT THERAPY

H. J. ROBERTS, M.D.

West Palm Beach, Florida

An ever-increasing problem that confronts many physicians is the management of bleeding episodes during long-term anticoagulant therapy in cases of myocardial infarction, stroke or other vascular diseases. Temporary cessation of the anticoagulant drug and substitution of vitamin K in small doses may not be adequate to control the bleeding, yet if large doses of vitamin K are given they will nullify the prophylactic effect of the anticoagulant. Clinics throughout the world have reported that the protection afforded by long-term treatment with an anticoagulant continues as long as the drug is administered, as judged by statistics on the mortality rate and the incidence of thrombo-embolic recurrences. For example, it has been shown that when anticoagulant therapy is stopped suddenly after continuous administration for one or more years the mortality rate tends to approximate that in untreated control groups (1).

This report concerns a new approach to the management and prophylaxis of anticoagulant-induced bleeding, using estrogens administered either orally or intravenously. The study stemmed from previous observations on the beneficial effects of estrogens in other bleeding disorders, as discussed later.

FACTORS INFLUENCING ANTICOAGULANT-INDUCED BLEEDING

For purposes of orientation it is pertinent to review certain considerations which should be borne in mind by the physician responsible for managing bleeding episodes in patients receiving long-term treatment with anticoagulants.

1. Patients who experience epistaxis or other forms of bleeding attributable to anticoagulant therapy usually can be maintained subsequently for months or years without additional hemorrhage by means of a slight modification of the initial regimen after the bleeding episode is controlled.

2. Anticoagulant-induced bleeding may occasionally be the result of dosage based on laboratory errors, mistakes on the part of the nursing staff, inadvertent excessive ingestion of the anticoagulant, the use of salicylates, antibiotics or alcohol, the phases of the menstrual cycle (2), or intercurrent illness, particularly hepatitis (3, 4). When the diet is poor in proteins there may be great variations in the prothrombin level; a diet rich in leafy green vegetables tends to increase the tolerance to anticoagulants (5). When recognized, removal or correction of most of these transitory influences will obviate recurrent bleeding. No significant changes in the prothrombin level occur in patients undergoing marked weight reduction with a properly conceived hypocaloric diet (6).

3. Drugs of the coumarin series should not be discontinued suddenly, in view of the risk of recurrent thrombosis and the high incidence of "rebound" thrombo-

embolism in the second to sixth week after omission (7). This problem is particularly challenging when patients receiving long-term anticoagulant therapy require extensive surgery and large skin grafts. Under such circumstances, surgeons are understandably anxious to keep local bleeding to a minimum.

4. Physicians with considerable experience in anticoagulant therapy occasionally have observed the paradox of the patient bleeding from one site while simultaneously experiencing thrombosis at another site. This is best explained by variations in local blood flow, capillary beds, platelets, and alterations involving aspects of the coagulation mechanism other than prothrombin concentration. Wessler and his colleagues (8) properly called attention to the fact that changes in prothrombin time and related determinations which specifically reflect a coagulation defect heretofore have been assumed to parallel the antithrombotic effect. In experiments involving the administration of serum fractions from donor dogs (in which the plasma prothrombic activity had been reduced by Dicumarol) to other animals in which the prothrombic activity was comparably depressed by Dicumarol, these investigators were able to demonstrate that: *a*) there was a clear-cut distinction between the coagulation defect and the antithrombotic effect of Dicumarol, and *b*) neither the one-stage prothrombic activity nor the prothrombin and convertin concentrations accurately reflected such antithrombotic activity. This appears to be the experimental counterpart of the clinical condition wherein thrombosis takes place in patients receiving Dicumarol when the one-stage prothrombin activity is below 15 per cent of the control value.

5. Most clinicians accept Wright's (19) rule-of-thumb for the optimal anticoagulant therapeutic zone, *viz*, prothrombin times ranging between 1½ and 2½ times the normal control value, provided the latter is between 12 and 18 seconds. Bleeding often takes place, however, in the absence of severe hypoprothrombinemia. For example, in one recent comparative study of four prothrombinopenic anticoagulant drugs, the prothrombin activity was considered to be within the therapeutic range in 19 of 23 patients who bled (10). (Since each of these drugs has virtually the same pharmacologic properties, it is unlikely that any one tends to induce bleeding more readily at comparable levels of prothrombin activity.) In another series comprising 70 patients receiving anticoagulants, there were 11 bleeding episodes when the prothrombin time was between 20 and 24.9 seconds and 3 bleeding episodes when the prothrombin time was less than 20 seconds (11). Nichol (12) observed that hematuria can occur in patients receiving long-term anticoagulant therapy when the prothrombin activity is only moderately depressed, and that it may not reappear in the same patient on other occasions when the prothrombin activity is reduced even more.

Such bleeding might be explainable in part by decreases in the other blood factors. Drugs of the Dicumarol-indanedione type generally are regarded as antivitamin-K in action, their effect being mediated through the mitochondria and resulting in depression of the synthesis of a number of coagulation proteins, particularly in the liver. There is impressive evidence that multiple coagulation

defects occur during long-term therapy, including those of prothrombin, Factor VII (proconvertin, SPCA), Factor IX (plasma thromboplastic component, PTC, Christmas factor), Factor X, plasma thromboplastin antecedent, the Hageman factor, and the Stuart-Prower factor (13, 14). The prothrombin time test may not be sensitive to depression of several important plasma procoagulants, notably Factor IX and antihemophilic globulin (Factor VIII). Accordingly, the thromboplastin generation test (TGT) and the one-stage partial thromboplastin time or PTT (which obviates the need for the poorly standardized serum reagent required in the thromboplastin generation test) have been recommended as better methods for indicating the total clotting ability of plasma when there is simultaneous depression of several of these coagulation factors. (For normal plasma, the time for coagulation in the PTT test is approximately 60 seconds.)

No specific clotting factor deficiency, however, can explain completely the hemorrhage in patients receiving anticoagulant therapy in whom prothrombin activity is at therapeutic levels (14). In discussing this problem of anticoagulant-induced hemorrhage, Brinkhous (15) summarized some of the current concepts as follows: "It appears that nature has provided man with a hemostatic mechanism in which there is a wide margin of safety. Three major components of this system have been emphasized: fibrin coagulation, platelets, both quantitative and qualitative aspects, and integrity of the smaller vessels, particularly in the microcirculatory system. It appears from both experimental and clinical experience that at least two of the three factors must be altered before significant hemorrhage occurs (Jaques). Since Dicumarol type therapy affects predominantly the fibrin coagulation mechanism, it may be that transient changes in the other two systems, possibly unrelated to the therapy itself, become the determining factor as to whether or not hemorrhage occurs in patients during controlled anticoagulant therapy."

Unfortunately, the laboratory technics currently available to most clinicians and hospitals are totally inadequate in enabling one to differentiate between patients who are potential vascular bleeders and those who are nonbleeders. The unreliability and the danger of dependence upon routine bleeding and clotting time values in children undergoing tonsillectomy and adenoidectomy has led to the de-emphasis and actual discard of these tests in several centers (16, 17). Various substances supposed to influence the "increased capillary permeability" (including ascorbic acid, the bioflavonoids, and rutin) have been recommended to decrease the risk of hemorrhage from oral anticoagulants, but with questionable success (18). In considering the limitations of the clotting time, bleeding time and capillary fragility tests, the following comments in a recent editorial (19) are pertinent "The consequences of using an unreliable test as a criterion for therapeutic results are or ought to be well known; they are referred to as regression towards the mean, centripetal drift, or the law of initial value. Persons who give extremely high or extremely low values on the first application of an unreliable test generally gravitate towards the normal when the test is

repeated. Any therapy can prove to have a 'normalizing effect' if the diagnostic test used is sufficiently unreliable. The history of the flavonoids in therapy can be explained largely in terms of the law of initial value."

6. A significant drawback to the administration of large doses of vitamin K_1 for the correction of reduced prothrombin activity in patients receiving anticoagulants is the difficulty in subsequent regulation of anticoagulant therapy (9). Reinduction of a therapeutic lowering of the prothrombin level after administration of a vitamin K preparation is more apt to be difficult when using prothrombin-depressant drugs characterized by a slow induction time and slow recovery (*e.g.*, bishydroxycoumarin) than when using those characterized by a short induction time and rapid recovery (*e.g.*, certain of the indanedione agents). The recommended dose of vitamin K_1 is 2.5 to 10 mg. orally for marked reduction of prothrombin activity without hemorrhagic phenomena (5 mg. if the prothrombin time is 45–60 seconds, and 10 mg. if it exceeds 60 seconds); 25 mg. orally or intravenously for minor bleeding; and 50 mg. or more intravenously in the case of severe hemorrhage (20–22). By employing small doses, early resumption of anticoagulant therapy is permitted without inducing refractoriness. Even with the long-acting preparations, vitamin K need not be used when the patient's prothrombin level is less than 10 per cent of normal, provided no bleeding is present. In individual patients, particularly those with hepatic disease, the response to vitamin K_1 may not be predictable. Olwin and Koppel (5) prefer the use of the active water-soluble vitamin K substances rather than vitamin K_1 or vitamin K_1 oxide, since the latter tend to render the patient more refractory to further anticoagulant therapy. They believe that all the prothrombin depressants (except diphenadione) can be neutralized effectively with these water-soluble vitamin K preparations.

7. The potential hazard of administering large doses of vitamin K or K_1 to patients with liver disease and hypoprothrombinemia has been appreciated only recently. Following the administration of 72 mg. of vitamin K (Hykinone) or 50 mg. of vitamin K_1 (Mephyton) in one such study, it was found that patients with advanced liver disease manifested either no response (or only a slight rise in prothrombin activity that usually disappeared after twenty-four hours) or a further decrease in the level of prothrombin (23).

8. When massive hematuria develops in patients receiving anticoagulant therapy, the administration of large doses of vitamin K or vitamin K_1 oxide may lead to massive coagulation of blood within the urinary tract, resulting in renal colic and oliguria. The increased tendency for clots to form in the renal pelvis of patients with gross hematuria has been related to the thromboplastic activity of the urine itself (12). This problem assumes further significance when it is recalled that the urinary tract represents the most common site of major and minor bleeding complicating anticoagulant therapy (12).

9. Transfusions of whole fresh blood, fresh plasma or lyophilized plasma reconstituted with 0.1 per cent citric acid solution also have been advocated for the treatment of excessive hypoprothrombinemia due to Dicumarol (24).

Unfortunately, these materials carry the risk of homologous serum hepatitis. (Blood or plasma stored in the fluid state is unsatisfactory owing to the loss of prothrombin activity.)

10. Occasionally, it is necessary to risk an increase in the dosage of anticoagulant to levels that are potentially hemorrhagic, since such large doses may be the only means of achieving relief. This is particularly true in patients with progressively severe coronary insufficiency and recurrent pulmonary embolism from clots originating in the lower extremities. Moreover, it is a general clinical impression that heavy smokers, heavy drinkers, those who are markedly overweight, and patients who are subjected to continual stress require larger dosages of anticoagulants.

11. The fear of operative and postoperative bleeding during long-term anticoagulant therapy in patients undergoing uncomplicated surgical procedures (*e.g.*, femoral vein ligations, amputations, and even appendectomy) is probably unwarranted, provided careful attention is directed to surgical hemostasis (25, 26). In two series of postoperative patients treated with Dicumarol (2307 and 3304 cases, respectively) there were no fatal hemorrhages, and only a few patients required transfusions (27). These observations also receive support from experiments in rats subjected to hypoprothrombinemia with Dicumarol (28); except for an increased incidence of delayed bleeding of no statistical significance, hemostasis was found to be normal (22).

The inherent risk of bleeding under these circumstances cannot be denied, however. Surgical procedures for peripheral arterial embolism probably can be carried out with greater safety in the patient who has received heparin rather than the prothrombin-depressant drugs Anticoagulant de-control in the surgical candidate with atrial fibrillation and a history of embolism should be gradually and completely accomplished by means of supplemental intravenous heparin. Olwin and Koppel (5) state that such operations can be carried out safely when the prothrombin level reaches 75 per cent or more under these circumstances—the heparin being continued until four hours prior to surgery. There is considerable variation in the prothrombin response to simple withdrawal of an oral anticoagulant. At least five days should be allowed after withdrawal of bishydroxycoumarin and three days after ethyl biscoumacetate, if the previous prothrombin values were in the desired therapeutic range. Heparin and the prothrombin-depressant are both resumed six hours postoperatively, the former being continued until the prothrombin level again is within the therapeutic range.

The use of intravenous estrogens both in anticipation of abnormal bleeding and in the treatment thereof, seems to add further safety to such a program of anticoagulant de-control. This applies to dental surgery (29) as well as to peripheral arterial surgery.

METHODS AND CLINICAL STUDIES

Intravenous estrogens were used in the management of 21 significant bleeding episodes in 16 patients personally followed over a four-year period in private

practice. In addition to epistaxis and hemoptysis (5 episodes), bleeding occurred from the urinary tract (6 episodes), hemorrhoids (2 episodes), the uterus (2 episodes), the upper gastro-intestinal tract (4 episodes), and into the skin (2 episodes). In most cases, no vitamin K preparation had been taken.

In 9 additional instances, the administration of intravenous estrogens was related to dental surgery (29).

The intravenous preparation employed was Premarin Intravenous.[1] This drug comes in the form of individual "Secules," each containing 20 mg. of estrogens in a naturally occurring, water-soluble conjugated form (expressed in terms of sodium estrone sulfate). Immediately prior to infusion the solution was slowly reconstituted by the addition of 5 ml. of sterile diluent containing 0.5 per cent phenol, U.S.P. (provided in an accompanying vial). The solution was then administered intravenously at a deliberately slow rate in order to obviate the occurrence of flushes or any unforeseen complications that might develop, *e.g.*, following injection of pharmacologically active medication into patients with cardiovascular disease. If necessary, a second injection was given twelve to twenty-four hours after the first. One or two such injections usually sufficed to control the bleeding.

The author has personally administered several hundred such infusions (other indications being severe prostatism and urinary stress incontinence in seriously ill patients with congestive heart failure, myocardial infarction and stroke, severe gastro-intestinal hemorrhage associated with portal hypertension, and the prevention and management of intraocular hemorrhage in patients with diabetic retinopathy), yet he has never observed any significant systemic, allergic or local inflammatory reactions (30, 31). Others have injected doses as high as 500 mg. of Premarin Intravenous within a 24-hour period without demonstrable deleterious effects (32). (A 21-year-old male patient with generalized bleeding due to aplasia of the bone marrow, currently under treatment, has received over 3000 mg. of this preparation for the control of bleeding without attributable complications.) Neither hyperestrogenic effects nor significant retention of sodium chloride and water were observed when short-term intravenous therapy was employed; patients with previous heart failure or intolerance to oral estrogens were carefully watched for development of these complications. Their absence probably can be best explained by the following: 1) rapid excretion of the exogenous hormone from the body, with little opportunity for it to exert action on either the target organs or on the kidneys, and 2) rapid metabolism of the intravenously administered estrogen and conversion into nonactive metabolites (33, 34).

The relatively prompt cessation of bleeding following intravenous estrogen therapy in most patients was impressive. It occurred even after considerable amounts of vitamin K or vitamin K_1 had been given orally or intramuscularly and after local packing of the nose or gums had proven ineffective. In many instances, hemostasis was evident within a few hours. In the majority of these cases, the anticoagulant therapy was resumed a few days after the bleeding

[1] Kindly supplied by Ayerst Laboratories, New York.

had stopped, and for the most part was continued without further bleeding episodes. Although treatment was on an out-patient basis, an attempt was made to keep the prothrombin time below 30 seconds.

An occasional patient exhibits striking sensitivity to anticoagulant drugs, and the prothrombin time may exceed 60 seconds for one week or longer following the standard initial dose. In 2 such patients, minor episodes of nasal and urinary bleeding were controlled by means of intravenous estrogens without resorting to a vitamin K preparation; anticoagulant therapy was subsequently and uneventfully resumed (see Case 15).

Even though the estrogen was effective in stopping hemorrhage, the prothrombin times determined at varying intervals after injection of estrogen into hypoprothrombinemic patients with spontaneous bleeding usually failed to demonstrate any significant change. Case 1 was a striking exception in this regard.

The standard one-stage prothrombin time determinations employing Simplastin were made by the same technician in all these studies, except when performed in the hospital; the control values generally ranged from 14 to 16 seconds. Facilities for detailed analysis of the clotting mechanism were not available; such analyses were carried out by Dr. Helen Glueck of the University of Cincinnati (see Discussion).

Oral estrogen therapy was continued or frequently instituted for varying periods of time following cessation of the bleeding, particularly in paramenopausal patients with coronary insufficiency receiving long-term anticoagulant therapy. At times, treatment for minor bleeding was carried out solely by the oral route, often entailing a mere increase in the maintenance dosage of the estrogen being taken. A blood cholesterol level repeatedly in excess of 300 mg. per 100 ml. was regarded as a further indication for prolonged estrogen treatment.

In several patients who appeared to benefit from concomitant oral estrogens, as manifested by a reduction or cessation of bleeding, placebos were given for varying lengths of time; these were identical in appearance to the 0.3-mg. and 1.25-mg. tablets of Premarin.

In 9 patients undergoing dental extractions, the usual procedure consisted of omitting the anticoagulant (Dicumarol, Liquamar or Coumadin) for three to five days preceding surgery. Premarin Intravenous was injected half an hour prior to extraction (29). No vitamin K or K_1 preparation was employed. In all patients, the immediate postoperative bleeding was minimal, despite residual hypoprothrombinemia. An additional dose of Premarin Intravenous was given in eight to twelve hours to 5 patients who had been hospitalized for extensive extractions or who subsequently manifested significant local oozing. The oral anticoagulant was resumed the day following dental surgery.

Although estrogens can produce anemia and aplasia of the marrow experimentally (35, 36), particularly in dogs and rats (monkeys appearing to be refractory), this has not proved to be a clinical deterrent in patients receiving large doses of estrogens intravenously and moderate doses by mouth. Similarly, although thrombocytopenia associated with estrogen therapy occasionally has been observed by others (37), it was not noted in this series.

The following are representative experiences in 15 patients:

CASE REPORTS

Case 1. Cutaneous bleeding controlled by oral and intravenous estrogens, with exacerbation during administration of a placebo

E. S., a 57-year-old female accountant, had been receiving long-term anticoagulant therapy for coronary insufficiency. Even with relatively small amounts of Liquamar (1.5 mg. daily), she experienced episodes of extensive ecchymoses and purpuric areas on the extremities. This necessitated reduction in the dosage of anticoagulant to nontherapeutic levels, followed in turn by an aggravation of angina pectoris.

Oral Premarin (0.3 mg. daily) was started, and the dosage of Liquamar was progressively increased from 1.5 mg. daily, to 1.5 mg. alternating with 3.0 mg. on Mondays, Wednesdays and Fridays. The average prothrombin time was 20 seconds. After five months on this program, there were only a few new small purpuric areas (attributable to the delicate skin tendency to easy bruising found in many women); this was in striking contrast to the pre-estrogen situation.

On January 19, 1960, without any other change in the program, the patient was given a placebo in place of her previous estrogen. By February 16, 1960, her body was covered with small petechiae and ecchymotic areas. No clotting was demonstrable with the prothrombin-time test even at three minutes on four trials. (The control prothrombin time and the values in 4 other patients, determined simultaneously, were within the anticipated range.)

Premarin by mouth was resumed and an injection of 20 mg. of Premarin Intravenous was given. No vitamin K preparation was administered. By the following day, the prothrombin time was 17.4 seconds. Several more petechiae had developed but there was no further frank bleeding. The pre-placebo regimen was resumed. Progressive resorption of the petechiae and ecchymoses ensued. No similar exacerbation has occurred to date (twelve months after resumption of the active hormone).

Case 2. Bleeding after dental extraction, controlled by intravenous estrogens

W. S., a 49-year-old engineer, was first seen in April 1956 with persistent angina pectoris and a functional gastro-intestinal syndrome. He subsequently had two myocardial infarctions necessitating hospitalization. Because of protracted severe chest pain, notwithstanding long-term anticoagulant therapy, he was subjected to pericardial poudrage with concomitant ligation of the internal mammary artery. Following his third myocardial infarction (which took place after the pericardial surgery), long-term anticoagulant therapy was resumed, having been discontinued prior to the cardiac surgery. He ultimately was able to return to his work as an industrial engineer for the first time in over two years.

The patient fared well with anticoagulant therapy, and no bleeding episodes occurred until one tooth was extracted. Prophylactic intravenous estrogens were not given. The anticoagulant (Liquamar) was withheld for several days before extraction, and good dental technique was used followed by local packing and the ingestion of four vitamin K_1 (Mephyton) tablets (20 mg.). Nevertheless, the operative site continued to bleed profusely for two days. The prothrombin time was 24 seconds. The author was called to see the patient the following night because of hemorrhage from the gum at the site of extraction. The patient was given 20 mg. of Premarin Intravenous. A pack containing a small amount of epinephrine also with applied. Within several hours, the bleeding had ceased completely. Subsequently, the maintenance anticoagulant dosage was resumed without incident.

Case 3. Estrogen therapy prior to dental extraction

L. H., a 71-year-old white female had been hospitalized six months previously for acute myocardial infarction. Thereafter she was treated with a maintenance dosage of anticoagulant therapy (Liquamar, 1.5 mg. daily and 3 mg. on Wednesdays and Saturdays), pentaery-

thritol tetranitrate (Peritrate), and 0.3 mg. of oral Premarin daily. The average prothrombin time was 21 seconds.

Then an upper molar required extraction. The anticoagulant was stopped for four days beforehand, and she received Premarin intravenously half an hour prior to the extraction. The operation was difficult, and there was the expected operative bleeding, but the postoperative course was remarkably free of further bleeding or oozing. Anticoagulant therapy was resumed the following day without incident. Several days later, the prothrombin time was 22.4 seconds.

Case 4. Hematuria controlled by intravenous estrogens

M. N., a 48-year-old housewife with coronary insufficiency, had been receiving long-term anticoagulant therapy with Dicumarol (50 mg. daily and 75 mg. on Fridays). There had been no evidence of bleeding for more than one year. The prothrombin time generally had ranged between 21 and 25 seconds. She also was receiving Premarin with meprobamate by mouth.

Following a sudden and unaccountable rise in the prothrombin time to 34.8 seconds, gross hematuria was noted for the first time. Anticoagulant therapy was stopped. A single injection of Premarin Intravenous effected prompt cessation of the macroscopic bleeding. The anticoagulant was resumed after a few days. For more than six months, to date, there has been no further clinical or microscopic hematuria.

Case 5. Hemoptysis controlled by intravenous estrogens

S. H., a 76-year-old lawyer was first seen because of persistent spitting of blood, of acute onset. Following a previous myocardial infarction, he had been maintained with Dicumarol by his northern internist. There had been no previous bleeding episodes. This patient also manifested prostatism, persistent pyuria, and moderate benign prostatic hypertrophy. His left kidney had been removed thirty years previously because of extensive formation of renal stones.

Within several hours after being given 20 mg. of Premarin Intravenous, there was no further hemoptysis. Dicumarol was continued without subsequent difficulty, the prothrombin time being maintained at approximately 20 seconds. Following the intravenous infusion of Premarin, the patient was impressed with the improvement in his ability to urinate. He had been receiving sulfonamide medication for a long period because of a urinary-tract infection that was resistant to most drugs. On several subsequent occasions, the relief afforded by intravenous Premarin lasted approximately three to four weeks. Following a brief respite, he would experience more prostatism, which again responded promptly to the estrogen. There was also gratifying symptomatic improvement during this time and more satisfactory control of the infection, attributable in part to the lessened urinary-tract obstruction.

Case 6. Hemoptysis controlled by intravenous estrogens

L. R., a 72-year-old housewife, had been treated for congestive heart failure following previous myocardial infarction. She progressed satisfactorily with maintenance dosages of digitalis, Peritrate, Liquamar, hydrochlorothiazide, and isocarboxazid (Marplan). There was a long-standing pulmonary apical infiltration; repeated chest films, however, showed no change. The prothrombin time had been maintained in the range of 20 to 25 seconds for five months with little difficulty. There followed an unexpected rise from 22 seconds to 36.6 seconds, associated with moderate brisk hemoptysis. There was no change in the clinical picture and no bleeding from other mucous membranes. Anticoagulant therapy was stopped.

Premarin intravenously effected a prompt diminution of the bleeding which gradually abated over the next several days. No acid-fast organisms were found in 3 specimens of sputum. Subsequently, there were no changes in the chest films and no recurrence of hemoptysis after ten months of resumed anticoagulant therapy.

Case 7. Hematuria due to complicating hepatitis controlled by intravenous estrogens

H. B., a 55-year-old female, was treated with bed rest and Peritrate following an initial bout of coronary insufficiency. Subsequently, long-term anticoagulant therapy was started because of persistent chest pain which prevented her from performing minor household chores. The patient fared well on this program. The prothrombin time ranged from 20 to 25 seconds. After six months of anticoagulant therapy, she noted that her urine had become very dark. The next value for prothrombin time was 41 seconds. The urine contained numerous red blood cells per high-power field. It was thought at first that the hematuria was secondary to an excessive anticoagulant effect *per se*.

The patient was given 20 mg. of Premarin Intravenous along with 5 mg. of vitamin K_1 oxide by mouth. When again seen two days later, she stated that the urine was still dark brown, but urinalysis did not reveal significant hematuria. Urobilinogen was present in large amounts and the patient was found to be mildly jaundiced. Then other clinical manifestations of hepatitis appeared. Recovery was uneventful, with conservative management.

In this case there is an added point of interest. The hematuria was due to hypoprothrombinemia resulting from the continued administration of an anticoagulant during the development of hepatitis. We have observed an almost identical train of events in another female patient with coronary heart disease and "subclinical" hepatitis who was receiving anticoagulant therapy (4). Accordingly, hematuria, or the persistence of urinary discoloration once hematuria has been controlled, offers a clue to the presence of complicating hepatitis in patients treated with anticoagulants for long periods of time.

Case 8. Rectal hemorrhage from diverticulitis controlled by intravenous estrogens and oral vitamin K_1

H. H., a 68-year-old painter with arteriosclerotic heart disease, had experienced two severe attacks of coronary insufficiency requiring hospitalization. Eighteen months after the second attack, anticoagulant therapy was stopped because of removal of a melanoma; within ten days the patient experienced a bout of thrombophlebitis. He had been taking maintenance doses of Liquamar for over two years, and the prothrombin time had generally ranged between 21 and 25 seconds. Massive gastro-intestinal bleeding then took place. The erythrocyte count fell rapidly to 3.2 million per cu. mm., the hemoglobin level to 10.3 Gm. per 100 ml., and the hematocrit to 31 per cent. Liquamar was stopped.

With three injections of Premarin Intravenous, vitamin K_1 by mouth, and anti-ulcer precautions, the intestinal bleeding ceased. The red blood cell count was rapidly restored with the aid of parenteral iron; no transfusions were administered. A barium enema demonstrated extensive diverticulosis and active sigmoidal diverticulitis.

Anticoagulants were later resumed following an acute anterior myocardial infarction. The prothrombin times averaged 23 seconds. There has been no rectal bleeding for five months since resumption of anticoagulant therapy.

Case 9. Rectal bleeding controlled by intravenous estrogens

D. M., a 37-year-old female, had been receiving long-term anticoagulant therapy (Liquamar, 3 mg. alternating with 4.5 mg. every other day) for progressive coronary insufficiency, as well as small oral doses of Premarin (0.3 mg. daily). Prothrombin time values had averaged 20 seconds for five months. Following a rectal fissure, there was massive rectal bleeding. Several hours previously, a prothrombin time value of 19.6 seconds had been obtained. Anticoagulant therapy was stopped.

Shortly after receiving an injection of Premarin Intravenous, the rectal bleeding ceased. Another intravenous injection of Premarin was given the next day. Anticoagulant therapy was subsequently resumed and there have been no further bleeding episodes for eight months, to date.

Case 10. Traumatic hematoma controlled by intravenous and oral estrogens

C. S., a 68-year-old white male with recurrent thrombophlebitis, pulmonary embolism, left bundle-branch block and symptomatic coronary insufficiency, had been maintained with long-term anticoagulation therapy after his last bout of thrombophlebitis. With Liquamar (3 mg. alternating with 1.5 mg. every other day), the prothrombin time was kept within the desired therapeutic range. For several years, he also had been taking diethylstilbestrol (5 mg. daily) for the control of a prostatic neoplasm.

After several uneventful months, the prothrombin time unaccountably rose to 34.8 seconds. At the same visit, it was noted that he had gained 7 pounds in weight. The dosage of Liquamar was reduced and he was given an injection of merethoxylline (Dicurin) procaine. Several days later, the prothrombin time had risen to 70 seconds, and a massive hematoma had developed over the right deltoid area (the site of the mercurial injection), with extensive ecchymoses over the right arm and forearm. He took 10 mg. of vitamin K_1, which previously had been given to him as an anticoagulant "antidote."

The dose of diethylstilbestrol was increased to 10 mg. daily and he received Premarin Intravenous daily for two days—the anticoagulant being stopped. Three days later, there had been striking reduction in the size of the arm. The prothrombin time was 19.0 seconds. Liquamar was resumed thereafter in a dosage of 1.5 mg. daily. No further difficulty has arisen over the ensuing eight months, and the prothrombin values have averaged 25 seconds.

Case 11. Bleeding from injury to small artery (during hypoprothrombinemia), controlled with intravenous estrogens

W. S. (Case 2), after the dental extraction, had an uneventful course over the next two years, during long-term anticoagulation therapy with Dicumarol. An attempt by the patient to discontinue therapy resulted in a severe exacerbation of coronary pain three weeks later. On June 24, 1960, the prothrombin time was 31.2 seconds; the patient was taking Dicumarol in a dosage of 100 mg. three times a week and 75 mg. four times a week. On June 30, 1960, he caught his little finger in an air-conditioning unit, and the lateral half of the nail bed was severed. Bleeding continued over the next twenty-four hours, notwithstanding local pressure. When seen at that time, there was persistent and profuse bleeding emanating from a small artery at the base of the wound. It continued in spite of local adrenaline packs, elevation of the extremity, and local pressure for an additional hour.

The patient was given Premarin Intravenous (20 mg.) and advised to continue local pressure with elevation of the arm after a special finger dressing was applied. The bleeding ceased within approximately three hours. The following morning, there was no further evidence of bleeding. The prothrombin time again was 31.2 seconds.

Case 12. Metrorrhagia controlled with intravenous estrogens

V. C., a 40-year-old female with recurrent angina pectoris of eight months' duration, had been receiving maintenance doses of Coumadin averaging 10 mg. daily, without incident. The prothrombin time repeatedly was in the range of 23 to 24 seconds. She also had hypertension (blood pressure 200/120 mm. Hg) and clinical and radiographic evidence of an aortic-arch syndrome with involvement of the left subclavian artery. Her menstrual periods always had been regular, were moderate in amount, and lasted three to four days. Suddenly she experienced severe menstrual bleeding with large clots, two weeks after a normal period. Five days previously, the prothrombin time had been 23 seconds. By the fourth day of active bleeding, it was still difficult to find a sufficient number of pads to absorb the blood. Anticoagulant therapy was stopped.

Approximately five hours after being given Premarin Intravenous (20 mg.) the bleeding stopped. There was a slight recurrence the following morning, with a prothrombin time of 23.6 seconds. After another intravenous injection of Premarin there was no further menstrual bleeding. The anticoagulant was resumed without incident two days later. Subsequent study of her pelvis failed to reveal any significant underlying pathologic condition.

Case 13. Conjunctival hemorrhage controlled by intravenous estrogens

H. H., a 64-year-old restaurateur, had been receiving long-term anticoagulant therapy following an acute myocardial infarction. He required 3.0 mg. of Liquamar daily to maintain a prothrombin time averaging 24 seconds. His course was completely uneventful for one year, until a massive spontaneous subconjunctival hemorrhage developed in the left eye. This also posed a cosmetic problem for him in his constant contact with the public. Liquamar was stopped. Within three days after receiving two intravenous injections of Premarin the hemorrhagic exudate had diminished strikingly. Anticoagulant therapy was resumed without incident thereafter. At no time during or following the bleeding was there any deviation from the maintenance prothrombin time.

Case 14, Conjunctival hemorrhage and subsequent hemoptysis associated with congestive heart failure—both controlled by intravenous estrogens

D. C., a 68-year-old retired broker, had been receiving long-term anticoagulation therapy following an acute myocardial infarction and concomitant congestive heart failure. A regimen of digitalis, restricted sodium, Liquamar, hydrochlorothiazide and other supportive measures was instituted. His subsequent course was remarkably uneventful, except for occasional angina. Prothrombin times generally ranged between 22 and 28 seconds.

No bleeding occurred until ten months after the initial cardiac episode, when he experienced a massive subconjunctival hemorrhage in the left eye following an attack of coughing due to acute bronchitis. The prothrombin time was 22.4 seconds at that time. With two intravenous injections of Premarin and omission of the anticoagulant for two days, there was striking resorption of the exudate within a week. No change in weight occurred.

This patient continued to do well for two months. He then became highly excited while watching a fight on television, and promptly suffered a classic attack of acute heart failure with profuse hemoptysis. The prothrombin time was 25.4 seconds. Anticoagulant was stopped for one day. Premarin Intravenous was administered, in addition to more digitalis, a parenteral mercurial diuretic, oxygen and a modified Karell diet. By the following day, hemoptysis had virtually disappeared; dyspnea was much less, and there had been a 5-pound diuresis. The prothrombin time was 25 seconds. Another intravenous injection of Premarin was given. There was no further recurrence of hemoptysis or gain in weight, even though the anticoagulant was withheld for *only* one day. The patient's course over the next two months was uneventful.

Case 15. Hematuria stemming from a single remaining kidney—controlled by intravenous estrogens

J. B., a 64-year-old retired advertising executive, suffered from long-standing severe coronary insufficiency and recurrent myocardial infarction. When first seen in consultation, his attacks of angina pectoris were increasing. Anticoagulation therapy had been tried elsewhere, and there had been considerable difficulty maintaining therapeutic levels. It was felt that the patient should be given another trial of long-term anticoagulant therapy. He also had mild congestive failure (dyspnea and predominant nocturnal angina) and was receiving digitalis and diuretics. He had undergone a nephrectomy ten years previously for a nonfunctioning atrophic kidney following urinary-tract bleeding, although from which side the bleeding had occurred was not clear.

With the usual priming dosage of Liquamar (*i.e.*, 27 mg.) the patient experienced marked hypoprothrombinemia (levels in the range of 70 seconds) for several days. There was no bleeding, however, until approximately two weeks after initiating anticoagulant therapy—at which time hematuria occurred. The prothrombin time was 31.5 seconds. There were no other manifestations of bleeding, but there was marked urgency of urination (although his prostate was not significantly enlarged).

Anticoagulant therapy was stopped, and the patient was given only Premarin Intra-

venous. The following day, no further hematuria could be detected grossly and only a few red blood cells were found in the urine. Concomitantly, the urinary urgency abated. A second intravenous injection of Premarin was given. By the following day, there was only a rare red blood cell in the urinary sediment. The level of blood urea nitrogen was 35 mg. per 100 ml., and the prothrombin time 30 seconds. The anticoagulant then was resumed in low dosage (average, 1.5 mg. daily). His clinical condition improved and the attacks of angina were greatly diminished. The dose of the anticoagulant was curtailed in order to keep the prothrombin time within 20 to 25 seconds. Premarin was started by mouth in a dosage of 0.3 mg. daily. There has been no further hematuria to date.

DISCUSSION

The problem of anticoagulant-induced bleeding

The magnitude of this problem is apparent from several reports. In one survey of anticoagulant therapy in acute myocardial infarction, 122 deaths attributable to anticoagulants were reported by 64 cardiologists (38). The sites of the hemorrhage were as follows: subarachnoid, 22; cerebral, 24; peptic ulcer, 20; gastro-intestinal (no localized lesion demonstrable at necropsy), 10; pericardium, 20; kidneys, 5; lungs, 2; and the retroperitoneal area, 2. In a 1949 survey encompassing approximately 15,500 patients, supplemented by his own experience, Nichols sought information from 136 physicians regarding the incidence of hemorrhage during anticoagulant therapy; he was able to cite 35 previously unreported fatalities attributable to anticoagulants (12). In yet another review of 227 patients managed with long-term anticoagulant therapy, Tulloch and Wright observed 70 hemorrhagic episodes in 43 patients (11). The major forms of bleeding in order of decreasing frequency were as follows: ecchymoses, hematomata, hematuria, epistaxis, hemoptysis, bleeding hemorrhoids, bleeding gums, melena, vaginal bleeding, hematemesis, excessive menstrual bleeding, cerebral hemorrhage, bleeding into the anterior chamber of the eye, acute hemorrhagic glaucoma, traumatic hemarthrosis and bleeding from the tongue.

The frequency of hemorrhagic complications from anticoagulant therapy—most of which are not reported—is also demonstrated by the findings in a review of 107 cases of fatal poisoning over a five-year period; Dicumarol was found to be the most common drug taken orally that resulted in death (39). Contributing causes to such mortality include incorrect diagnoses (*e.g.*, dissecting aortic aneurysm misdiagnosed as acute myocardial infarction, or cerebral hemorrhage misdiagnosed as cerebral thrombosis), the performance of a lumbar sympathetic block or spinal tap in the presence of persistent anticoagulant activity, and the presence of carcinoma. Anticoagulant therapy must be regarded as a calculated therapeutic risk in patients having a significant degree of hepatic or renal insufficiency, ulcerative lesions of the gastro-intestinal tract, purpura of any type, blood dyscrasias (particularly thrombocytopenia) with a bleeding tendency, subacute bacterial endocarditis, recent operations on the brain or spinal cord, or severe hypertension, and in obstetrical cases approaching term. Although genetically-determined increased susceptibility to Dicumarol has been observed in rabbits, such an hereditary background has not as yet been demonstrated in patients who exhibit profound hypoprothrombinemia during oral anticoagulant therapy.

The foregoing lists do not exhaust the potential complications stemming from anticoagulant-induced bleeding. For example, large hematomas following intramuscular injection of an anticoagulant can cause prolonged sciatica or peroneal nerve involvement with partial paralysis of the leg (18) (also see Case 10). Another less known complication of oral anticoagulant therapy is hemoperitoneum, which can simulate other acute abdominal disorders (40). In a patient with extensive cutaneous and intraperitoneal hemorrhage, intravenous Premarin appeared to be a valuable adjunct in promptly terminating the bleeding (41). In patients with previously asymptomatic intra-abdominal adhesions, anticoagulant-induced bleeding may result in acute intestinal obstruction on a mechanical basis (41).

It is not amiss to remind the clinician that unanticipated genito-urinary, gastro-intestinal or bronchial hemorrhage developing during maintenance therapy with standard doses of an oral anticoagulant in patients with "safe" prothrombin times should suggest the possibility of either an underlying malignant lesion (42) or unrecognized hepatitis (4). This issue is particularly deserving of emphasis when relatively prompt and complete cessation of the bleeding cannot be achieved by vitamin K or estrogen medication.

The pharmacologic basis of estrogenic hemostasis

There is still a paucity of clinical and experimental information dealing with the mechanism of action of this "physiologic hemostat." Historically, it was demonstrated in 1933 that abnormal bleeding times in newborn infants could be lowered by parenteral administration of crystallized estrin (theelin) (43).

That there are several potential facets of such action is suggested by the value of intravenous and oral estrogens in the treatment of massive gastro-intestinal hemorrhage associated with portal hypertension (30), recurrent intra-ocular hemorrhage associated with diabetic retinopathy (31), epistaxis associated with hemorrhagic telangiectasia (44, 45), corticosteroid-induced ecchymoses (46), delayed post-traumatic hemorrhage, functional uterine bleeding, and bleeding following tonsillectomy, prostatectomy and ophthalmic surgery (47–50). The case of an elderly hemophiliac in whom massive hemorrhage following dental extraction was uncontrollable until the administration of estrogens intravenously is also on record (51). It appears that conjugated estrogens exert their influence both on the blood clotting mechanism and, more significantly, on the capillary bed. The rapid increase in concentration of estrogens following intravenous injection is probably an important factor in promoting coagulation of the blood.

One mechanism of action proposed to account for estrogen-enhanced coagulation involves the sharp rise in Factor V (plasma Ac-globulin, proaccelerin, labile factor). This change has been noted in dogs within the first fifteen minutes following the intravenous infusion of estrogenic steroids, reaching a peak in approximately ninety minutes, and returning to a normal concentration by four hours (52). An increase has been noted in prothrombin concentration following intravenous administration of estrogens in dogs, together with a decrease in the antithrombin activity of the plasma. The latter action might increase the amount of thrombin made available, and accordingly enhance the coagulability of blood

(52). Other evidence that intravenous estrogen can influence the coagulation mechanism stems from the interesting observation that this steroid produces a definite decrease in the prolonged clotting time observed in dogs subjected to an acute radiation syndrome—most notably between thirty and sixty minutes following injection (53).

The author usually could not detect any measurable alteration in prothrombin concentration following intravenous administration of Premarin in patients with induced hypoprothrombinemia who had begun to bleed. Detailed studies in humans specifically relating to the effect of intravenous Premarin on the individual factors involved in the coagulation process have been carried out recently by Dr. Helen Glueck (54). An increase in Factor V was found, but no demonstrable change in the prothrombin time, the prothrombin content, Factor VII, the bleeding time, the clotting time, or the clot retraction (54). It is of interest that the values for Factor V in the dog are normally high, whereas those in the human (10–15 units per ml.) are among the lowest for all the species that have been tested (55). Accordingly, in man, the depression of the level by only a few units under certain situations might have an important bearing upon bleeding; conversely, any agent that could induce an elevation in the concentration of Factor V might prevent or control bleeding (52).

Estrogens also exert a significant effect on the capillary bed. The following are clinical examples: (*a*) The author and others (44, 45) have observed the suppression of recurrent epistaxis in hemorrhagic telangiectasia, both cyclically in relation to the menses and following the oral and parenteral administration of estrogens. (*b*) Massive spontaneous epistaxis not responding to anterior and posterior packing, vitamin C, vitamin K, ice packs, thrombin and fibrin foam, subsequently controlled by intravenous estrogens (44, 47); following the arrest of epistaxis by estrogen therapy, the open vessel still can be seen even though no blood is escaping (47, 48); concomitantly, there is a change in the color of the congested cyanotic vessels to a more normal hue. (*c*) A colleague (56) has repeatedly been able to terminate bouts of hemoptysis in a patient with mitral stenosis by intravenous administration of Premarin. (*d*) In a patient with severe thrombocytopenia due to almost total aplasia of the bone marrow, significant success both in treating and preventing widespread hemorrhages into the skin and mucous membranes was achieved for more than four months by means of daily intravenous injections of Premarin in doses ranging from 20 to 60 mg., whereas large doses of dexamethasone, vitamin C, vitamin K, citrus bioflavonoid compound with vitamin C, and multiple transfusions of fresh blood had proved ineffective. Furthermore, it was possible to perform three uncomplicated bone marrow aspirations in this patient under such a pharmacologic "umbrella"—at a time when the platelet count was 11,000 per cu. mm., the bleeding time over 20 minutes, and clot retraction almost nil at three hours. (*e*) Intravenous estrogens have proved to be effective in the management of fibrinolysis during and after surgical procedures, particularly prostatic operations (57).

Perhaps the most significant current studies on the hemostatic action of estrogens are those dealing with the effect on the mucopolysaccharides of the ground

substance; these polysaccharides have an important bearing upon capillary permeability and fragility. By means of colloidal iron and other stains, Burn and Schiff (58) repeatedly have demonstrated a progressive change (lasting several hours) from the sol state to the gel state in the tissue mucopolysaccharides of hamsters, monkeys and man following the intravenous injection of Premarin. This alteration appears to be due to an increase both in the quantity and polymerization of the mucopolysaccharides, and it occurs equally in males and females. Preliminary observations by the same investigators also indicate that the enhanced resorption of hemorrhagic residues by estrogens may be explainable in part by an effect upon a spreading factor. Other hemostatic mechanisms to explain the effect of estrogen therapy have been advanced (59, 60), including serotonin-like activity and the neutralization of a vascular toxin. There is evidence, based on the inhibition of hyaluronidase wheals following the injection of Premarin, that this agent acts on the ground substance to limit the activity of hyaluronidase (60b).

Alterations in the integrity of the microvascular bed are significant in the genesis of anticoagulant-induced bleeding (15). In both animals and man dying acutely after administration of massive doses of Dicumarol, the histologic picture has been one of dilatation of the capillaries and the small arteries and veins (61, 62).

Hench (63) has speculated upon the important clinical and pathogenetic potentialities of major cortisone "ebb-tides" as related to the onset, exacerbation and renewal of certain rheumatic and collagen inflammations. Similarly, important premonitory estrogen "ebb-tides" may be related to the pathogenesis of various unexplained hemorrhagic manifestations. It is known that estrogens act catalytically and in low concentration at a critical level of cell metabolism in a wide variety of tissues. For example, diethylstilbestrol strongly inhibits the diphosphopyridine nucleotide oxidation normally carried out by enzymes in a variety of mammalian tissues, tumors and microorganisms. The agent of this inhibition has been localized in skeletal muscles to DPNH cytochrome-C reductase (64). Since the nucleotide specific electron transport pathways represent critical control points in metabolic reactions, this inhibitory effect (shared by estrogens and other hormonally active steroids) enables small amounts to exert significant metabolic influences, even in tissues devoid of steroid enzymes.

Another possible mechanism of this estrogenic effect may be an indirect action by way of the adrenocortical hormones. Several recent reports indicate that estrogen administration can influence adrenocortical steroid metabolism. For example, the oral administration of estrogens will elevate the level of free plasma 17-hydroxycorticosteroids, delay the plasma clearance of exogenous cortisol, and reduce the urinary excretion of conjugated 17-hydroxycorticosteroids (65). (These effects have been attributed in part to the induced increase in cortisol-binding by transcortin.) Administration of estrogen to males and females also can decrease the excretion of other urinary steroids of both gonadal and adrenal origin, including androsterone, etiochoanolone, dehydroisoandrosterone, 11-oxyketosteroids, ketogenic steroids, and pregnanetriol (66). A competitive

inhibition between cortisol and estrogens at an enzymatic level is likely, since the defect in biotransformation can persist for weeks following discontinuance of the estrogen. It may involve either the level of the co-enzyme TPNH or the levels of TPNH-linked steroid dehydrogenases in the liver that are necessary for enzymatic inactivation of estrogen and cortisol. For example, the predominant initial reaction in the metabolism of cortisone is a reduction of the C-11 ketone to an 11-hydroxyl function (cortisol).

Cortisone and corticotropin cause a decrease in capillary permeability and a reduction in prolonged bleeding time in certain hemorrhagic states, notably "pseudohemophilia" (67). Furthermore, the corticosteroids may induce hypercoagulability of the blood as a result of thrombocytosis and decreased plasma fibrinolytic activity (possibly mediated through the inhibition of the action of serotonin in promoting fibrinolysis) (13).

Hemostatic prophylaxis with estrogens

The protective action afforded by oral estrogens against bleeding in patients receiving long-term anticoagulation therapy for underlying coronary heart disease has been inferred several times. The recurrence of extensive cutaneous bleeding in Case 1 and of brisk rectal bleeding in another patient (R. McC.) after administration of identical-appearing placebos instead of Premarin, and the prompt control of such bleeding upon resumption of the active estrogen, merit such a conclusion. Additional support is lent by the ability of anticoagulant-treated patients to undergo dental extractions with minimal bleeding following prophylactic intravenous estrogens (29). The following case summary also exemplifies the apparent protection against anticoagulant-induced bleeding afforded by oral estrogens:

Case 16. M. B., a 46-year-old female, was admitted to the hospital with acute coronary insufficiency in June 1958. She responded well to a program of oxygen, Peritrate, heparin, and subsequently to anticoagulant (Liquamar). Oral Premarin was also given because of a concomitant severe anxiety state and a menopausal reaction. The hormone was continued for the ensuing six months, the dose being decreased to 1.25 mg. three times weekly because of slight menstrual irregularities and the favorable clinical course. The maintenance dose of Liquamar was 1.5 mg. daily, supplemented by an additional 1.5 mg. twice or thrice weekly. The oral estrogen was then discontinued for three weeks because of the patient's feeling of well-being and the desire to reduce her medication to a minimum. The prothrombin time had consistently ranged between 18 and 23 seconds.

At the time of her next visit, the prothrombin time was in excess of 2 minutes. She had experienced several nosebleeds the previous day. Shortly after the intravenous injection of Premarin, the resumption of oral estrogens, and temporary cessation of the anticoagulant, the epistaxis subsided completely, even though the prothrombin time remained longer then two minutes for an additional four days. Liquamar (1.5 mg. daily) was resumed, and the patient progressed satisfactorily during the ensuing five months, without recurrence of bleeding.

In certain patients with coronary insufficiency, carotid or basilar artery insufficiency, and recurrent thrombophlebitis with pulmonary embolism, the underlying disorder can be completely controlled clinically by adequate anticoagula-

tion, but the treatment has to be kept at a suboptimal level because of repeated bleeding episodes. In our experience with several such patients, prolonged oral estrogen therapy, supplemented at the first sign of bleeding with intravenous estrogens, has proved to be most effective. Unfortunately, such a method of treatment is not always possible because of the development of edema or of postmenopausal vaginal bleeding in a minority of patients receiving oral (but not intravenous) estrogens.

Intravenous or oral estrogens may possibly prevent or minimize the risk of hemorrhagic pericarditis in anticoagulant-treated patients with acute myocardial infarction and a pericardial friction rub. Studies along these lines are in progress.

Intravenous estrogens also may prove to be of prophylactic value in patients with hypoprothrombinemia due to either anticoagulant therapy or underlying liver disease when a deep needle puncture is deemed necessary for diagnosis (*e.g.*, pericardiocentesis or liver biopsy) or for treatment (*e.g.*, sympathetic block).

Concomitant prophylaxis of atherosclerosis with estrogens

There is clear-cut statistical evidence that bilateral oophorectomy prior to the natural menopause results in an increased incidence of clinical coronary disease and peripheral atherosclerosis when compared with the incidence in women undergoing hysterectomy without castration (68). Determination of the excretion of estrone, estradiol-17β, and estriol in 96-hour specimens of urine from 17 premenopausal patients with breast cancer revealed approximately the same decrease in estrogen excretion following ovarian irradiation as after bilateral oophorectomy (69). Furthermore, studies of urinary estrogen excretion indicate that the postmenopausal ovary retains a small but important secretory function and is the major site of the postmenopausal production of estrogen (70). There is a highly significant difference between the urinary estrogen excretion of postmenopausal women and that of castrated women, the former being approximately twice as great as the latter.

On the basis of these observations, the author now routinely administers small doses of an oral estrogen to the majority of his female patients with coronary insufficiency or myocardial infarction, especially those in their 30's and 40's. The possibility of producing endometrial hyperplasia and perturbing vaginal bleeding in the menopausal or postmenopausal female is accepted as a reasonable therapeutic risk. Women whose ovaries have been removed or irradiated are particularly benefited by such replacement therapy. Clinically, the same benefit applies to women who have undergone hysterectomy without oophorectomy, presumably because the blood supply to the ovaries has been markedly decreased. Oral estrogen therapy exerts a favorable effect in these patients, not only because it ameliorates associated tension states, but because it influences certain underlying metabolic derangements. Some of the evidence is as follows:

1. *The abnormal concentrations of circulating lipid and lipoprotein return to the normal range, i.e.*, there is a decrease in the serum level of total cholesterol, an elevation in the phospholipids, and a fall in the cholesterol-phospholipid ratio,

even without modification of the dietary fat intake. This is also evident when estrogenic substances are administered orally to men with myocardial infarction (71–74). Diminution in the serum concentration of beta lipoproteins in the S_f 12–20 and 20–100 classes following a single intravenous dose of Premarin in a patient with coronary insufficiency has been reported (75). The effect on the serum cholesterol and phospholipid levels tends to be maximal and maintained after ninety days of therapy, little difference being observed between the effects of ethinyl estradiol (Estinyl), diethylstilbestrol, Manvene and Premarin. Prolonged administration of estrogens does not appear to lessen this metabolic effect, and no tolerance or resistance to the hormone has been observed (66). In addition to the marked reduction in serum lipid and lipoprotein concentrations, striking disappearance of xanthomatous lesions has been induced by oral estrogen therapy in patients with primary hypercholesterolemic xanthomatosis or idiopathic hyperlipemia (75–77). Relatively small doses of methyltestosterone can counteract completely the biochemical effects of estrogens when the two are administered simultaneously (75). The administration of progesterone to men with coronary artery disease and hypercholesterolemia has failed to produce significant changes in the level of serum cholesterol, β-lipoprotein, and the cholesterol-phospholipid ratio (78).

2. In experiments relating to the production of atherosclerosis in chickens, Stamler, Peck and Katz (79) were able to *prevent or reverse atherosclerosis* induced in the coronary arteries (but not in the aorta) by means of estrogens. Although large doses of estrogen (diethylstilbestrol) added to a normal diet increased atherogenesis in the chick, when combined with cholesterol the estrogen seemed to counteract the cholesterol-induced atherogenic effects. Pathologic studies in humans also lend support to the thesis that estrogens are a factor in the atherogenic process—or more accurately their absence is a factor—and bear a more specific relationship to coronary atherosclerosis than to aortic atherosclerosis (80). Patients who have received estrogens over prolonged periods for either prostatic or mammary carcinoma appear to exhibit less extensive atheromatous invasion of the arteries. Decreased atherosclerosis is demonstrable in patients with cancer of breast in association with ovarian stromal hyperplasia and hyperestrinism (81).

3. Interest has been redirected recently to the observation that *estrogens can stimulate the phagocytic activity of reticuloendothelial cells*, which activity in turn plays an important role in cholesterol metabolism (82). This mechanism could explain the ability of estrogens to enhance the resorption of local subcutaneous implants of absorbable gelatin sponge saturated with cholesterol, without any detectable alteration in the level of serum cholesterol (83). The possibility of such an influence of estrogens on human coronary atherosclerosis—namely, the production of local alterations in the coronary vessels in the absence of any demonstrable changes in the serum cholesterol level, phospholipid-cholesterol ratio or lipoprotein pattern—demands the attention of clinicians. The fact that there is a marked increase in cellular activity in the media of blood vessels as a result of estrogen stimulation has prompted the observation that the gonads may be the "Achilles heel" in the aging process (84).

Estrogen therapy is not being employed widely at present in male patients because of the tendency to anorexia, nausea, vomiting, impotence, depression, and enlargement of the breasts if large doses (*e.g.*, 10 mg. of Premarin or 1.0 mg. of ethinyl estradiol daily) are administered for prolonged periods. Much smaller doses, such as 0.2 mg. of ethinyl estradiol for periods of two years, can rectify the abnormal serum lipid and lipoprotein pattern with infrequent side-effects (78). By administering estrogen therapy cyclically (for three weeks followed by one week without medication) to nonhysterectomized women and to men with idiopathic hyperlipemia and idiopathic hypercholesterolemia, Adlersberg (85) was able to maintain low serum cholesterol and beta-lipoprotein levels with only mild adverse effects. Gastric distress, nausea and general discomfort are less apt to be associated with large dosages of Premarin than with large dosages of ethinyl estradiol, even though the effects on the breasts and sexual desire and function are essentially the same with equivalent doses (76). In middle-aged men with coronary atherosclerosis, although testicular function is depressed, there is no apparent detriment to thyroid or adrenal function with dosages of Premarin averaging 10 mg. daily for periods exceeding one year (74). In spite of prolonged estrogen therapy, the basic masculine psychologic traits of such patients remain unchanged.

SUMMARY

The intravenous administration of conjugated estrogens (Premarin Intravenous) is of considerable clinical benefit in the management of patients who bleed during long-term anticoagulant therapy. These bleeding episodes may be spontaneous or associated with dental extractions and various surgical procedures. Intravenous estrogens may be safely and effectively administered either alone or in conjunction with a vitamin K preparation.

The rationale for such therapy is discussed. This approach enables the clinician to continue anticoagulant therapy following control of isolated bleeding episodes—a factor in treatment that is particularly significant when considered in terms of the following: 1) the greater chances for survival of patients with coronary disease when treated with anticoagulants; 2) the development of a "rebound hypercoagulability state" if anticoagulants are stopped suddenly; and 3) the difficulty in subsequent resumption and regulation of anticoagulant therapy when large doses of vitamin K or K_1 have been administered previously.

Long-term oral estrogenic therapy appears to prevent or reduce anticoagulant-induced bleeding, while concomitantly influencing the underlying atherogenic process.

In view of the increasing indications and widespread use of long-term anticoagulant therapy, it is hoped that others will attempt to confirm these observations and extend the present limited information pertaining to the mechanisms of the hemostatic action of estrogenic substances.

REFERENCES

1. WRIGHT, I. S.: Coronary artery disease: progress and problems, *J. Am. Geriatrics Soc.* **8:** 237, 1960.

2. Bay, E. B.; Adams, W. R.; Jones, R. J.; Page, R. G., and Seide, M.: The use of anticoagulant drugs in ambulatory patients, *Circulation* **9:** 741, 1954.
3. Kliesch, W. F.; Young, P. C., and Davis, W. D., Jr.: Dangers of prolonged anticoagulant therapy in hepatic disease: diathesis and intercurrent acute hepatitis, *J.A.M.A.* **172:** 223, 1960.
4. Roberts, H. J.: Anticoagulant therapy in hepatic disease, *J.A.M.A.* **172:** 1856, 1960.
5. Olwin, J. H., and Koppel, J. L.: Practical aspects of long-term anticoagulant therapy, *A.M.A. Arch. Int. Med.* **100:** 842, 1957.
6. Roberts, H. J.: Effective long-term weight reduction: experiences with Metrecal, *Am. J. Clin. Nutrition* **8:** 817, 1960.
7. Toohey, M.: Vitamin K_1 in anticoagulant therapy, *Brit. M. J.* **1:** 1020, 1954.
8. Wessler, S.; Ballon, J. D., and Katz, J. H.: Studies in intravascular coagulation. V. A distinction between the anticoagulant and antithrombotic effects of Dicumarol, *New England J. Med.* **256:** 1223, 1957.
9. Wright, I. S.: Present status of anticoagulant therapy in the treatment of myocardial infarction; the use and misuse of anticoagulants; an evaluation of new anticoagulants, their indications and dosage, *Ann. Int. Med.* **43:** 942, 1955.
10. Rodman, T.; Ryan, C. S.; Pastor, B. H.; Hollendonner, W. J., and Harrison, E.: A comparative study of four prothrombinopenic anticoagulant drugs. II. Clinical study, *Am. J. Med.* **27:** 415, 1959.
11. Tulloch, J., and Wright, I. S.: Long-term anticoagulant therapy: further experiences, *Circulation* **9:** 823, 1954.
12. Nichol, E. S.: The risk of hemorrhage in anticoagulant therapy, *Ann. Western Med. & Surg.* **4:** 71, 1950.
13. Koppel, J. L., and Olwin, J. H.: Physiologic aspects of intravascular clotting, *Am. J. Cardiol.* **4:** 585, 1959.
14. Boyles, P. W.: Hemorrhagic diathesis associated with long-term anticoagulant therapy, *Southern M. J.* **53:** 441, 1960.
15. Brinkhous, K. M.: Discussion of paper by Boyles (14).
16. Diamond, L. K., and Porter, F. S.: Inadequacies of routine bleeding and clotting times, *New England J. Med.* **259:** 1025, 1958.
17. Fox, S. L.: Bleeding following tonsillectomy and adenoidectomy, *Bull. School Med. Univ. Maryland* **38:** 134, 1957.
18. Nichol, E. S.; Phillips, W. C., and Jenkins, V. E.: Anticoagulants in coronary heart disease, *Med. Clin. North America* **38:** 399, 1954.
19. Editorial: Bleeding and clotting times, *J.A.M.A.* **172:** 63, 1960.
20. Schirger, A.; Spittel, J. A., Jr., and Ragen, P. A.: Small doses of vitamin K_1 for correction of reduced prothrombin activity, *Proc. Staff Meet., Mayo Clin.* **34:** 453, 1959.
21. Shoshkes, M.; Robins, B., and Yelin, G.: Orally administered phytonadione in bishydroxycoumarin-induced hypoprothrombinemia, *J.A.M.A.* **165:** 330, 1957.
22. Cosgriff, S. W.: The effectiveness of an oral vitamin K_1 in controlling excessive hypoprothrombinemia during anticoagulant therapy, *Ann. Int. Med.* **45:** 14, 1956.
23. Steigmann, F.; Schrifter, H.; Yiotsas, Z. D., and Pamukcu, F.: Vitamin K therapy in liver disease; need for a reevaluation, *Am. J. Gastroenterol.* **31:** 369, 1959.
24. Cosgriff, S. W.; Cross, R. J., and Habif, D. V.: Excessive hypoprothrombinemia due to "dicumarol": its treatment with lyophilized plasma, *J.A.M.A.* **138:** 405, 1948.
25. Littman, J. K., and Brodman, H. R.: Surgery in the presence of the therapeutic effect of Dicumarol, *Surg., Gynec. & Obst.* **101:** 709, 1955.
26. Van der Veer, J. B.; Parker, A. P., and Boyer, F. R.: Emergency appendectomy in a patient receiving anticoagulants for myocardial infarction, *J.A.M.A.* **149:** 1307, 1952.
27a. Allen, E. V.; Hines, E. A., Jr.; Kvale, W. F., and Barker, N. W.: The use of Dicumarol as an anticoagulant: experience in 2,307 cases, *Ann. Int. Med.* **27:** 371, 1947.
b. Wise, W. D.; Loker, F. F., and Brambel, C. E.: Effectiveness of Dicumarol prophylaxis against thromboembolic complications following major surgery; a four-year survey: 3,304 cases, *Surg., Gynec. & Obst.* **88:** 486, 1949.

28. Zucker, M. B.: Platelet agglutination and vasoconstriction as factors in spontaneous hemostasis in normal, thrombocytopenic, heparinized and hypoprothrombinemic rats, *Am. J. Physiol.* **107:** 280, 1948.
29. Roberts, H. J.: Estrogenic control and prevention of bleeding following dental extraction during long-term anticoagulant therapy, *J.A.M.A.* (in press).
30. Roberts, H. J.: The control of gastrointestinal hemorrhage by combined steroid therapy, (submitted for publication).
31. Roberts, H. J.: Estrogenic control of diabetic retinopathy, with particular reference to intraocular bleeding, *J. Am. Geriatrics Soc.* (submitted for publication).
32. Hertz, R.; Tullner, W. W.; Westfall, B. B.; Morrow, A. G., and Emge, M. K.: Intravenous administration of massive dosages of estrogen to human subject; blood levels attained, *Proc. Soc. Exper. Biol. & Med.* **72:** 187, 1949.
33. Preedy, J. R. K., and Aitken, E. H.: The effect of estrogen on water and electrolyte metabolism. III. Cardiac and renal disease, *J. Clin. Invest.* **35:** 443, 1956.
34. Dignam, W. S.; Voskian, J., and Assali, N. S.: Effects of estrogens on renal hemodynamics and excretion of electrolytes in human subjects, *J. Clin. Endocrinol. & Metab.* **16:** 1032, 1956.
35. Tyslowitz, R., and Dingemanse, E.: Effect of large doses of estrogens on the blood picture of dogs, *Endocrinology* **29:** 817, 1941.
36. Vollmer, E. P., and Gordon, A. S.: Effect of sex and gonadotropic hormones upon the blood picture of the rat, *Endocrinology* **29.** 828, 1941.
37. Cooper, B. A., and Bigelow, F. S.: Thrombocytopenia associated with the administration of diethylstilbestrol in man, *Ann. Int. Med.* **52:** 907, 1960.
38. Russek, H. I., and Zohman, B. L.: Anticoagulant therapy in acute myocardial infarction. A survey of specialists' opinions concerning indications, results and dangers, *Am. J. M. Sc.* **225:** 8, 1953.
39. Flaxman, N.: Drug fatalities, *J.A.M.A.* **147:** 377, 1951.
40. Mendelsohn, S. N., and Iglauer, A.: Acute abdominal condition due to bishydroxycoumarin (Dicumarol) poisoning, *A.M.A. Arch. Int. Med.* **92:** 760, 1953.
41. Roberts, H. J.: Intestinal obstruction due to Dicumarol-induced hemoperitoneum, *J. Florida M. A.* (in press).
42. Stern, S., and Dreskin, O. H.: Bleeding from occult disease during anticoagulant therapy, *Angiology* **8:** 337, 1957.
43. Hirst, J. C.: The influence of female sex hormone upon blood coagulation of the newborn, *Am. J. Obst. & Gynec.* **26:** 217, 1933.
44. Waller, J. V.: Hemorrhagic telangiectasia treated with stilbestrol, *Ann. Int. Med.* **44:** 204, 1956.
45. Koch, H. J., Jr.; Escher, G. C., and Lewis, J. S.: Hormonal management of hereditary hemorrhagic telangiectasia, *J.A.M.A.* **149:** 1376, 1952.
46. Roberts, H. J.: Estrogenic control of corticosteroid-induced cutaneous bleeding, *A. M. A. Arch. Dermat.* (in press).
47. Jacobson, P.: Spontaneous hemorrhage: clinical entity, with special reference to epistaxis, *A.M.A. Arch. Otolaryng.* **59:** 523, 1954.
48. Jacobson, P.: A unified concept of spontaneous bleeding, *West. J. Surg., Gynec. & Obst.* **63:** 711, 1955.
49. Greenblatt, R. B., and Barfield, W. E.: The effect of intravenous estrogen in uterine bleeding, *J. Clin. Endocrinol.* **11:** 821, 1951.
50. Menger, H. C.: Estrogen given parenterally to control epistaxis and hemorrhage after adenoidectomy: preliminary report, *J.A.M.A.* **159:** 546, 1955.
51. Whittington, P. B., Jr.: Control of bleeding with intravenous estrogens, *J. Am. Dent. A.* **53:** 595, 1956.
52. Johnson, J. F.: Changes in plasma prothrombin, Ac-globulin, and antithrombin concentration following intravenous administration of estrogens, *Proc. Soc. Exper. Biol. & Med.* **94:** 92, 1957.
53. Michaelson, S.: Personal communication.

54. Glueck, H.: Personal communication.
55. Murphy, R. C., and Seegers, W. H.: Concentration of prothrombin and Ac-globulin in various species, *Am. J. Physiol.* **154:** 134, 1948.
56. Smith, C.: Personal communication.
57. Lorimer, W. S., Jr.: Hemorrhagic disorders occurring during and after surgical operation, *Ann. Surg.* **151:** 85, 1960.
58. Schiff, C., and Burn, H. F.: The effect of intravenous estrogens on ground substances, *A.M.A. Arch. Otolaryngol.* (in press).
59. Jacobson, P.: Hormonal management of spontaneous hemorrhage, *Virginia M. Monthly* **84:** 396, 1957.
60a. Jacobson, P.: Spontaneous hemorrhage: a clinical entity: with special reference to the bleeding state, pathology and hemostasis, *Virginia M. Monthly* **85:** 548, 1958.
b. Wayne, L., and Glueck, H.: Personal communication.
61. Shlevin, E. L., and Lederer, M.: Uncontrollable hemorrhage after dicoumarol therapy, with autopsy findings, *Ann. Int. Med.* **21:** 332, 1944.
62. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the hemorrhagic agent, 3,3′-methylenebis (4-hydroxycoumarin). IV. The pathologic findings after the administration of Dicumarol, *Am. J. Path.* **20:** 651, 1944.
63. Hench, P. S.: The ebb-tides of cortisone waves: their clinical and pathogenetic significance. Presented at the 41st Annual Session of the American College of Physicians, San Francisco, April 6, 1960.
64. Yielding, K. L., and Tomkins, G. M.: Steroid hormone inhibition of reduced diphosphopyridine nucleotide oxidation. Presented at the 41st Annual Session of the American College of Physicians, San Francisco, April 7, 1960.
65. Wallace, E. Z., and Carter, A. C.: Studies on the mechanism of the plasma 17-hydroxycorticosteroid elevation induced in man by estrogens, *J. Clin. Invest.* **39:** 601, 1960.
66. Herrmann, W. L.; Schindl, I., and Bondy, P. K.: The effect of estrogen on steroid levels in plasma and urine. Abstract No. 55, Program of the Forty-First Meeting of The Endocrine Society, Atlantic City, June 4-6, 1959, p. 43.
67. Jacobson, B. M.: Effects of cortisone and corticotropin on prolonged bleeding time: treatment in certain hemorrhagic states (pseudohemophilia), *A.M.A. Arch. Int. Med.* **92:** 471, 1953.
68. Robinson, R. W.; Higano, N., and Cohen, W. D.: Increased incidence of coronary heart disease in women castrated prior to the menopause, *A.M.A. Arch. Int. Med.* **104:** 908, 1959.
69. Diczfalusy, E.; Notter, G.; Edsmyr, F., and Westman, A.: Estrogen excretion in breast cancer patients before and after ovarian irradiation and oophorectomy, *J. Clin. Endocrinol. & Metab.* **19:** 1230, 1959.
70. Paulsen, C. A.; Leach, R. B.; Sandberg, H.; Sheinfeld, S., and Maddock, W. O.: Function of the postmenopausal ovary. Comparison of urinary estrogen and gonadotropin excretion and response to administration of FSH in postmenopausal and ovariectomized women, *J. Am. Geriatrics Soc.* **6:** 803, 1958.
71. Oliver, M. F., and Boyd, G. S.: The influence of the sex hormones on the circulating lipids and lipoproteins in coronary sclerosis, *Circulation* **13:** 82, 1956.
72. Steiner, A.; Payson, H., and Kendall, F. E.: Effect of estrogenic hormone on serum lipids in patients with coronary arteriosclerosis, *Circulation* **11:** 784, 1955.
73. Marmorston, J.; Moore, F. J.; Magidson, O.; Kuzma, O., and Lewis, J. J.: Effects of long-term estrogen therapy on serum cholesterol and phospholipids in men with myocardial infarction, *Ann. Int. Med.* **51:** 972, 1959.
74. Robinson, R. W.; Higano, N.; Cohen, W. D.; Sniffen, R. C., and Sherer, J. W., Jr.: Effects of estrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis, *Circulation* **14:** 365, 1956.
75. Gitman, L., and Greenblatt, I. J.: Effect of intravenously administered estrogen in cardiovascular disease, *Angiology* **4:** 502, 1953.

76. Russ, E. M.; Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma, *Am. J. Med.* **19:** 4, 1955.
77. Feldman, E. B.; Wang, C., and Adlersberg, D.: Effect of prolonged use of estrogens on circulating lipids in patients with idiopathic hyperlipemia or idiopathic hypercholesteremia, *Circulation* **20:** 234, 1959.
78. Oliver, M. F., and Boyd, G. S.: Endocrine aspects of coronary sclerosis, *Lancet* **2:** 1273, 1956.
79. Stamler, J.; Peck, R., and Katz, L. N.: Experiences in assessing estrogen antiatherogenesis in the chick, the rabbit, and man, *Ann. New York Acad. Sc.* **64:** 596, 1956.
80. Spain, D. M., and Bradess, V. A.: Post mortem studies on coronary atherosclerosis in one population group, *Dis. Chest* **36:** 397, 1959.
81. Rivin, A. U., and Dimitroff, S. P.: The incidence and severity of atherosclerosis in estrogen-treated males, and in females with a hypoestrogenic or a hyperestrogenic state, *Circulation* **9:** 533, 1954.
82. Heller, J. H.; Meier, R. M.; Zucker, R., and Mast, G. W.: The effect of natural and synthetic estrogens on reticuloendothelial system function, *Endocrinology* **61:** 235, 1957.
83. Spain, D. M., Aristizabal, N., and Ores, R.: Effect of estrogens on resolution of local cholesterol implants, *A.M.A. Arch. Path.* **68:** 30, 1959.
84. Masters, W. H.: Endocrine therapy in the aging individual, *Obst. & Gynec.* **8:** 61, 1956.
85. Adlersberg, D.: Hormonal influences on the serum lipids, *Am. J. Med.* **23:** 769, 1957.

PHYSICAL PROBLEMS OF OLDER PEOPLE*

ROBERT H. DOVENMUEHLE, M.D.,** E. W. BUSSE, M.D.† AND E. G. NEWMAN, M.D.‡

Department of Psychiatry, Duke University Medical Center, Durham, N. C.

There are many indications from statistical studies that there is an increase in the frequency and severity of chronic illnesses among the older people in our society.

In Leavell and Clark's textbook of preventive medicine (1) it is indicated that host factors associated with aging result in a greatly increased prevalence rate of long-term illnesses involving circulatory impairments, metabolic dysfunctions, arthritides, and neoplasms. In referring to the National Health Survey published in 1940, it is stated that regarding chronic disease or impairment lasting three or more months, half of such cases occurred in persons over 45 years of age, consisting of less than one-third of the population. There were indications that the proportion increased with advancing age. This particular study showed that disability amounting to invalidism affected only 10.8 per thousand persons aged 30 to 44 years, 55 per thousand aged 65 to 74 years and 101 per thousand aged 85 years and over.

Some of the major causes of disability and death from long-term illnesses become accentuated in the older age groups, according to Leavell and Clark (1). The 10 leading causes of disability in persons aged 65 and over (Baltimore Survey) were: heart disease (excluding rheumatic), arthritis, hypertensive vascular disease, nephritis, tuberculosis, diseases of bones and joints (except tuberculosis and arthritis), accidents, diabetes, cancer, and eye diseases. These data came from a five-year survey with monthly visits (1).

The 5 leading causes of death in 1956 in persons aged 65 years and over indicate that many of the leading causes of disability also cause most of the deaths in this age group. Taken from Public Health Service statistics (2) these were: diseases of the heart, cerebral hemorrhage and other vascular lesions effecting central nervous system, cancer and other malignant neoplasms, general arteriosclerosis, and all accidents.

* The data from which this paper was drawn stem from the project "The Effect of Aging Upon the Central Nervous System—A Continued Study of the Interrelationships Between Psychological, Physiological, and Social Factors in the Human Aging Process," by Dr. Ewald W. Busse, M.D., Principal Investigator. Investigations by the authors referred to in this article were supported by NIH Grants, M900, M2109 and H3582.

The authors express their appreciation to a number of their colleagues: Dr. W. D. Obrist, Project Co-ordinator, Dr. C. R. Nichols, Assistant Investigator, and Mrs. M. S. King, in charge of statistical processing.

** Research Co-ordinator, Center for the Study of Aging; Assistant Professor of Psychiatry, Duke University.

† Director, Center for the Study of Aging; Chairman, Department of Psychiatry.

‡ Instructor in Psychiatry.

In the discussion on sickness surveys in Haven Emerson's textbook on administrative medicine (3), it is pointed out that all types of surveys are limited either in the amount and accuracy of information available, or in terms of populations covered.

The present report concerns a limited group of older subjects who are active community members. Extensive medical, social and psychologic data are available on all subjects.

DEFINITION OF GROUP

As a part of a large study of the physiologic, psychologic and sociologic interrelationships of the effect of aging upon the central nervous system (4), we participated in the examination of 260 community volunteer subjects past the age of 60. These subjects were volunteers solicited from Golden Age groups, top-level business and professional people, and their neighbors and friends. Special efforts had to be made to obtain sufficient numbers of very old people for the investigation because the more feeble persons in the community did not volunteer readily for two days of research examinations. Many of these subjects participated specifically because they had heard that a complete physical examination was given during the study. However, most of them were actively functioning and were maintaining themselves independently in the community. Some claimed never to have had previous medical contact.

This group, when impressionistically compared with a group of hospitalized and a group of institutionalized older people also examined for research purposes, seemed physically and psychologically much more intact.

Our total sample of 260 subjects was distributed as shown in Table 1. It will be noted that more than half the subjects were in the 65–74 year age group—a factor which might affect the trends associated with aging in our study. In 9 cases we did not have sufficient information on which to base a physical functional rating.

PHYSICAL FUNCTIONAL RATINGS

Because of the importance of physical health in the concerns of our older citizens, a method was developed for rating the functional physical status of each subject. This was based in part on an extensive medical history, physical and neurologic examinations, and laboratory studies included in the routine series of research investigations. The 6 possible ratings on this scale are shown in Table 2.

This scale is modified and adapted from those in use by the United States Army and Veteran's Administration for rating disability. For our purposes, social limitation is defined as any restriction upon activity or communication involved in usually possible social activities for the particular subject. Sometimes this is a hypothetical "normal" situation, but often is reinforced by specific information regarding daily activity. For example, a rating of 30–50 per cent social incapacity would be given in the event of arthritic immobilization severe enough to prevent the subject from pursuing usual interests at church and at civic clubs but still permitting enjoyment of social intercourse with vis-

iting friends. On the other hand, limitation of vision and hearing to the point where understandable social relationships with others were practically terminated, would call for a rating of complete incapacitation.

Industrial capacity included useful occupations, whether performed for pay or not, since most of our subjects were retired. For example, a person with arthritic limitation who could not possibly get to a place of work or of part-time hobby activity if located outside the home, would be rated as seriously disabled. If, in spite of this limitation the person was able to engage actively in productive work around the home, he would not be rated as completely disabled.

Psychiatric limitations on ability to perform were not considered in conjunction with this rating. Only the physical aspects of the individual's potentiality for social and industrial activity were assessed.

THE PROBLEM

On the basis of physical functioning it was believed possible to demonstrate differences between sexes, races, socio-economic and age groups. If such differences could be demonstrated, it might be possible to determine whether or not higher and lower functioning groups are afflicted by similar illnesses, but of differing severity; or whether they are afflicted most severely by certain illnesses which have differential significance in terms of disability factors.

TABLE 1

Distribution of 260 Subjects on the Basis of Socio-economic Status, Sex, Race and Age

Lower Socio-economic Group (Golden Age Club members, etc.)			Higher Socio-economic Group (Top-level Business & Professional People)		
	Males	Females		Males	Females
White	44	47	White	42	42
Negro	31	34	Negro	9	11

Age Grouping					
Age range (yrs.)	61–64	65–69	70–74	75–79	80+
No. of subjects	47	72	69	39	33

TABLE 2

Physical Functioning Ratings

Condition	Rating
No pathology or limitation	0
Disease present. No limitation of social or industrial function	1
Limitation, 20% or less	2
Limitation, 21–50%	3
Limitation, 51–80%	4
Limitation, over 80%	5

METHODS

In order to accomplish this objective, it was necessary to keep our sample carefully matched with regard to variables other than those under direct examination. This was done by keeping all of the factors, except the one under consideration, in the exact proportions in which they appeared in the total sample.

The process of matching on a proportionate basis reduced somewhat the total universe of subjects available for each consideration (Figs. 1–4). Throughout the statistical work attempts were made to include the maximal universe of subjects available to the particular consideration.

SOCIO-ECONOMIC COMPARISON

In considering the socio-economic differences in groups matched proportionately for age, sex and race it was found that fewer limitations on physical functioning were present in persons of higher socio-economic status (Fig. 1). There were only 15 subjects with a physical functional rating of either 4 or 5 in this matched sample, whereas there were 22 with such a rating in the entire community group. Although this indicates some caution in accepting the significance of such a finding as applied to the upper range of disability, there is no question about the comparability in the lower ranges of the scale which indicate more adequate functioning. Forty-two of 47 subjects in the entire group who had no disease appeared in this particular sample. Of those who had disease without disability, 63 of 76 subjects appeared in this sample.

COMPARISON ON THE BASIS OF AGE

When subjects younger than 70 and older than 70 years of age were compared in a group matched for sex, race and socio-economic variables, the distribution

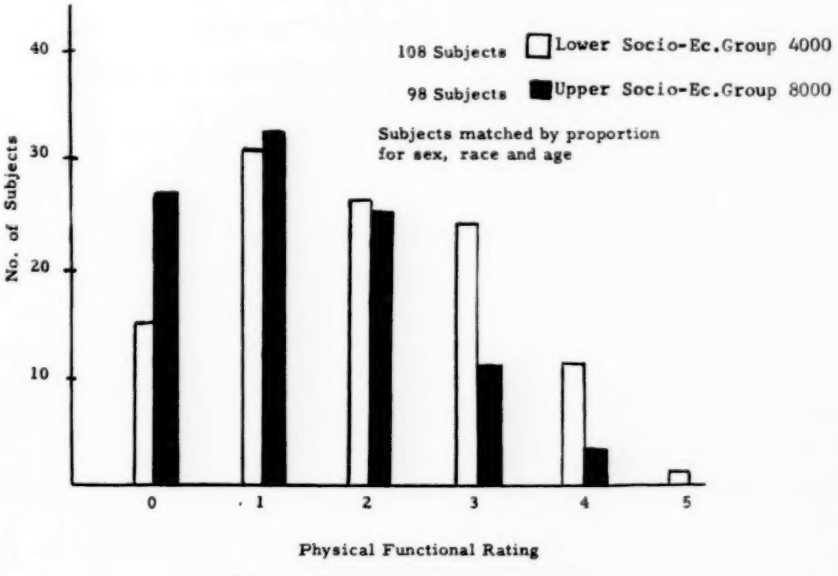

FIG. 1. Socio-economic comparison

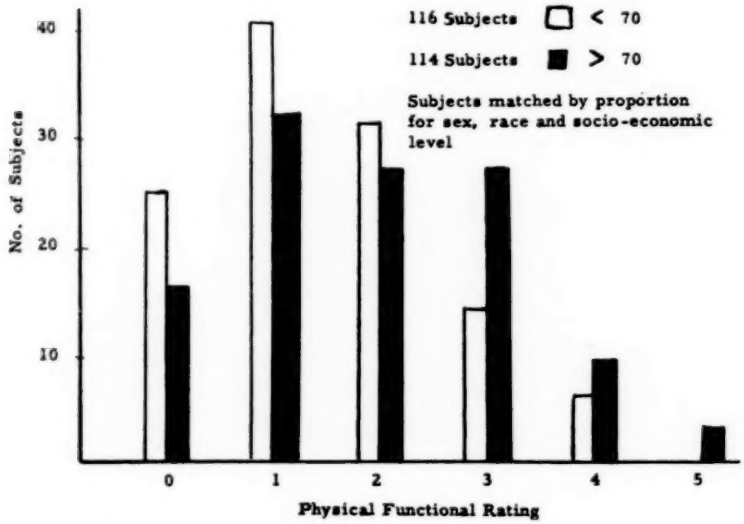

FIG. 2. Comparison on the basis of age (above or below 70 years)

was comparable to that in the larger group of subjects (Fig. 2). Those under 70 were less likely to have limitation of capacity according to the physical functional rating.

COMPARISON ON THE BASIS OF SEX

A comparison of males and females in a group matched for race, age and socio-economic condition indicated no significant differences (Fig. 3). Again this group was comparable to the entire sample of community subjects in terms of the distribution of physical functional ratings.

COMPARISON ON THE BASIS OF RACE

White subjects were compared with Negro subjects in a group matched proportionately for age, sex and socio-economic condition (Fig. 4). The matched group contained only 28 subjects who had no disease and no disability, but otherwise it was quite comparable to the total community group.

INCIDENCE OF DISEASE

Thus, there was a distinct difference between various socio-economic and age groups regarding current physical capacity. It was decided to limit the initial study of disease incidence in these groups to conditions known to be highly prevalent in the older age group. Table 3 shows the conditions that appeared more frequently in our lower socio-economic group. Some of these conditions also were more prominent in the older group than in the younger group.

Eisdorfer (5) found that combined impairment of hearing and vision had the greatest adverse effect on psychologic functioning, with a hearing defect alone having a pronounced effect. Since impairment of vision and hearing are common in elderly people, it was thought that the incidence of these disorders might be

reflected in the characteristics of the groups. However, there was no significant difference on the basis of hearing impairment as judged from the medical interview.

Vision was considered normal if the best eye, with correction if necessary, had vision up to 20/30. Vision between 20/50 and 20/100 was rated as impaired, and vision of less than 20/100 in the best eye was rated as grossly impaired. On this basis, there was significant differentiation between various socio-economic and age groups in our subjects.

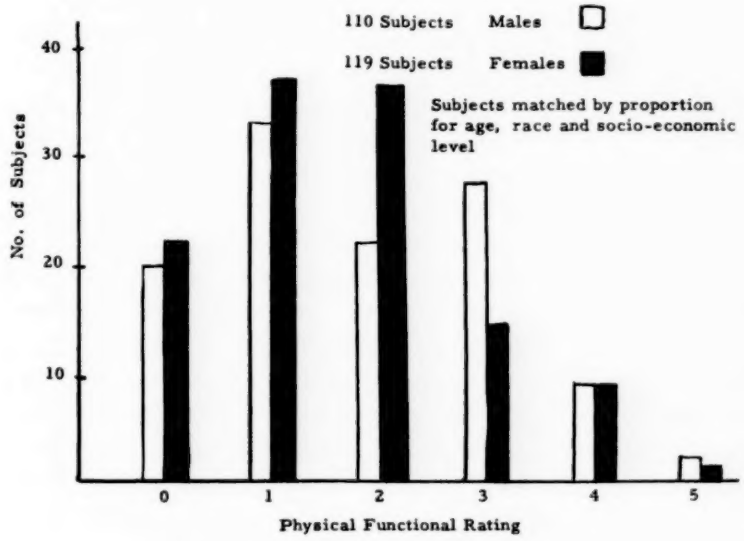

FIG. 3. Comparison on the basis of sex

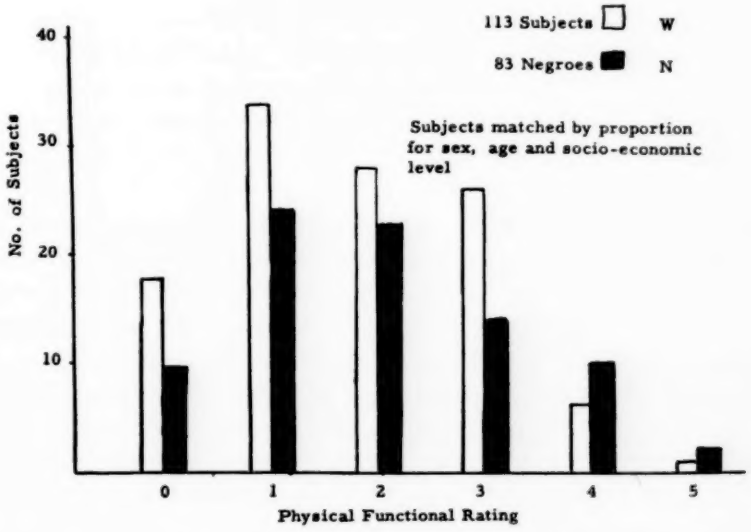

FIG. 4. Comparison on the basis of race

TABLE 3

Conditions Appearing More Frequently in the Lower Socio-economic Group

Condition	P Value
Impairment of vision	$P < .001$
Arteriosclerosis	$P < .05$
Cardiovascular disease	$P < .05$; especially in 70+ age group ($P < .05$)
High systolic blood pressure	$P < .05$; especially in 70+ age group ($P < .02$)
High diastolic blood pressure	$P < .02$; especially in 70+ age group ($P < .01$)
Pulmonary disease	$P < .02$; especially in 70+ age group ($P < .05$)
Limitation of joint movement due to arthritis	trend only

Disorders of the vascular apparatus were common in our community group; 70 subjects had moderate or severe arteriosclerosis. The criteria for moderate arteriosclerosis was absence of pulsations in the pedal arteries and limitation of exercise because of symptoms due to vascular constriction in the legs and/or cardiac or pulmonary phenomena. Severe arteriosclerosis was indicated by a verified history of cardiac disease and strokes. Contrary to the findings of others in relation to the blood cholesterol level (6), we found no differentiation of age groups regarding the incidence of this condition but there was a significant differentiation of socio-economic groups on this basis. There was an association between arteriosclerosis and cardiovascular disease, including arteriosclerotic heart disease and hypertensive heart disease combined. The incidence of cardiovascular disease of all kinds was higher in the lower socio-economic group, especially in persons past the age of 70.

This relationship, however, did not influence any relationship between cardiac status and group membership. Patients with a history of decompensated cardiac disease and/or clinical evidence of mild to severe cardiac failure were not statistically more frequent in either group. This may be attributable to the small number of cases, since only 23 subjects in the entire sample showed any evidence of decompensation either by history or by physical examination, and only 9 of these had any evidence of cardiac failure at the time of examination for the research study.

There was no distinct relationship with obesity. Although we had rough clinical ratings of obesity it seemed more desirable to utilize an index of surface area calculated from the weight and height. On this basis, there was only a slight trend for persons past the age of 70 in the lower socio-economic group to have larger surface areas. This was not considered a significant difference.

The clear relationship to arteriosclerosis indicated the possibility of characteristic group differences regarding both systolic and diastolic blood pressure. We chose a systolic blood pressure of 150 mm. Hg as the dividing line. The lower socio-economic group clearly had a higher proportion of cases within the upper range of blood pressure. This was especially true for people over 70 in this group. A similar situation pertained with respect to diastolic blood pressure, with 90

mm. Hg as the dividing line. It is noteworthy that in the entire sample, the diastolic blood pressure was between 90 and 100 mm. in 93 subjects, between 101 and 110 mm. in 39, and between 111 and 150 mm. in 39. There were 85 subjects in whom the systolic blood pressure was between 160 and 190 mm., and 48 in whom it was over 190 mm.

Electrocardiograms were available on 81 of the subjects from the community sample; in 55 there was some evidence of abnormality. For the purposes of this study no attempt was made to analyze these deviations. There was no significant relationship between electrocardiographic abnormalities and any of the other factors considered in this study.

Pulmonary disease, chiefly emphysema, is a relatively frequent accompaniment of aging. Among 40 subjects with some kind of pulmonary disease in the sample of 260 persons, 37 had emphysema regardless of what other pathologic lesion may have been involved. There was only 1 case of asthma uncomplicated by other disease. The occurrence of pulmonary disease was clearly related to socio-economic status, and especially so in subjects aged 70 and over.

An outstanding cause of illness in elderly people is arthritis. In the sample of 260 subjects, 92 had some form of arthritis, excluding traumatic. Fifty-three of these had osteoarthritis varying from mild to severe; 8 had rheumatoid arthritis, inactive or very mild; and 31 had undifferentiated arthropathy. There were no cases of gouty arthritis. No significant relationship could be found between arthritis and socio-economic condition or age. However, there was a trend toward more severe limitation of joint motion in the lower socio-economic group; the limitation included the joints of the upper extremity, lower extremity, hands, back and neck. Mild limitation in one or more areas was present in 81 of the 260 subjects, and moderate to severe limitation in 71.

DISCUSSION

There are several possible explanations for the higher disease frequency invariably associated with the lower socio-economic status.

The method of obtaining subjects by recruiting volunteers may have caused a bias in the sample with regard to the number of people with chronic illness from the lower socio-economic group. However, it has been ascertained that there were essentially no differences between the two groups in their reasons for coming, especially as concerns the possibility of medical examination or treatment. In all likelihood there was randomization of factors influencing both groups, so that conclusions from data on these subjects have sufficient validity to be used in formulating hypotheses for further experimental study.

Socio-economic classification involves many complex factors. Among them are education, occupational status and income. In addition, there are differences in the degree of familism (7). Investigations are now in progress to determine which of these factors involved in socio-economic rating could account for the greatest degree of variance in the results of this study. In general, the factors most heavily influencing the pattern of a person's living most likely influence his health status in old age.

The increase in incidence of many of these chronic illnesses with aging agrees with the findings of many previous studies. In view of the significantly different life expectancies of males and females, whites and Negroes, it is surprising that no significant differences in these respects were found in our study. Morbidity statistics do not necessarily relate directly to life expectancy, since illnesses may be of varying duration prior to the intervention of death. Since our sample is being followed longitudinally, mortality data will eventually be available.

Mayer and Hauser's (8) study of life expectation in Chicago for the years 1880 to 1940 indicated that the highest economic groups had significantly greater life expectancy than the lowest economic groups. The difference was seven and a half years between upper-income and lower-income white males and females, and six years between upper-income and lower-income Negro males and females in 1940. There was a spread of approximately eighteen years between the highest-income whites and the lowest-income Negroes. However, the gap constantly narrowed from 1920 onward. Although life expectancy studies are not necessarily revealing concerning morbidity statistics as reported on our sample, it is possible that the lack of a significant difference between whites and Negroes regarding physical functional capacity indicates that the gap has closed to this extent. Woodbury (9) quotes Children's Bureau statistics to the effect that infant mortality is related in inverse fashion to income or otherwise-determined economic status of the parents. Thus, it is also possible that the gap in life expectancy observed by Mayer and Hauser was largely on the basis of increased infant mortality in the lower socio-economic groups. If true, one would not expect as great a difference in the older age groups.

SUMMARY

The factors of socio-economic status, age, race and sex have been examined in relation to physical functional capacity in a group of 260 community volunteers past the age of 60.

Differences in physical capacity were apparent in relation to socio-economic status and age, but not in relation to sex or race.

Subjects, whether younger or older, or whether of high socio-economic status or low, could not be differentiated on the basis of different patterns of illness. Rather, certain illnesses caused more disability in older subjects of lower socio-economic status.

Impairment of vision, arteriosclerosis and cardiovascular disease, elevated systolic and diastolic blood pressures, pulmonary disease, and arthritic limitation of joint motion were observed more frequently in the lower socio-economic group.

REFERENCES

1. Leavell, H. R., and Clark, E. G.: Textbook of Preventive Medicine. New York, McGraw-Hill, 1953, p. 629.
2. Summary of Health and Vital Statistics. U. S. Department of Health Education, and Welfare, Public Health Service, Washington, D. C., June, 1958.
3. Emerson, H. (ed.): Administrative Medicine. New York, Thos. Nelson & Sons, 1951, p. 1007.

4. Dovenmuehle, R. H., and Busse, W. W.: Studies of the processes of aging: a review of the findings of a multidisciplinary approach, *Brit. J. Physical Med.* **1:** 100 (May) 1956.
5. Eisdorfer, C.: The effects of sensory decrement on Rorschach performance in an aged population. Doctoral Dissertation, University Microfilms, Ann Arbor, Michigan (in press).
6. Nichols, C. R., and Obrist, W. D.: Relation of serum cholesterol level to age, race, and sex in a community group of elderly people, (abstract) *J. Gerontol.* **13:** 442 (Oct.) 1958.
7. Brown, R. G.: Family structure and social isolation of older persons, *J. Gerontol.* (in press).
8. Mayer, A. J., and Hauser, P.: Class differentials in expectation of life at birth, *Rev. de l'Inst. Internat., de Statistique* **18:** 200, 1950; reprinted in Bendix, R., and Lipset, S. M.: Class Status, and Power. Glencoe, Illinois, The Free Press, 1953, pp. 281–284.
9. Woodbury, R. M.: Infant mortality in the United States, *Ann. Am. Acad. Political & Social Sc.* **188:** 94 (Nov.) 1936.

USE OF A NEW PSYCHIC ENERGIZER (MARPLAN) IN AN OLD AGE HOME: DOUBLE BLIND STUDY*

RAYMOND HARRIS, M.D.† AND WOLFGANG E. HOELSCHER, M.D.‡

The Department of Medicine, Ann Lee Home, and St. Peter's Hospital, Albany, N. Y.

Many elderly people, especially those long confined to an institution by age or illness, have some form of psychiatric disorder arising from functional brain disease, an organic brain lesion or a subtle disintegration of the psyche accelerated by the apathy and dull routine of institutional living. Manifesting extreme sadness, difficulty in thinking, irritability, weakness, fatigue and loss of appetite and initiative, they become depressed. Extremely depressed patients may suffer from delusions and hallucinations of an auditory or visual nature. When such a depression is associated with a marked degree of anxiety, the patient may respond with increased motor activity; this is the so-called agitated depression.

The potentially suicidal or destructive aged are generally transferred to a mental hospital. The depressed, apathetic, disoriented patients with chronic brain syndrome due to senility, cerebral arteriosclerosis, infections such as syphilis and tuberculosis, or toxic damage from alcohol and avitaminosis, may remain in the custodial sections of the home. They require numerous staff personnel to feed, wash and care for them, and they live out the rest of their lives in this protected environment. Such patients often continue to deteriorate, exhibiting progressive mental regression, retardation and confusion.

At the Ann Lee Home we became interested in these patients and their problems several years ago during our early work with reserpine in hypertension. Although primarily concerned with the effect of reserpine on blood pressure, we incidentally noted its value in the patients' psychiatric complaints (1). Subsequently we studied various drugs to determine if they would help the mental health of our residents. With the advent of iproniazid (Marsilid)[1] and other psychic energizers, it was thought that this type of compound might be potentially useful in the aged, provided the drawbacks did not outweigh the benefits. The side-effects of Marsilid therapy are well-known (2–7). However, the newly developed analog of iproniazid—isocarboxazid (Marplan)[2]—was reported to be safe (8–10). After reviewing the clinical and laboratory data obtained with Marplan in younger persons (11–16), we decided to evaluate it in our elderly patients.

* Presented at the 12th Annual Meeting of the Gerontological Society, Inc., November 12, 1959, Detroit, Michigan.

† Assistant Medical Director and Attending Cardiologist, Ann Lee Home; Chief of Cardiology, St. Peter's Hospital.

‡ Interne, St. Peter's Hospital.

[1] Marsilid® is a product of Hoffman-La Roche Inc., Nutley, N. J.

[2] Marplan®; active medication and placebo kindly supplied by Dr. J. Campbell Howard of Hoffman-La Roche Inc., Nutley, N. J.

CLINICAL MATERIAL AND METHODS

The residents originally selected were all males with a variety of somatic and psychic complaints, depression or confused behavior. We tried to include only those who had definite depressions and who were apathetic and withdrawn, regardless of age. About half were in the special wards reserved for chronic brain syndrome patients who required help constantly. Many had serious physical handicaps in addition to their mental illnesses.

A double blind experimental design was set up. Initially these 40 patients were divided alternately into two groups, X and Y, by the physician in charge of the project. The physician then ordered tablets A (placebos) and B (Marplan, one 10-mg. tablet three times daily) to be given according to the following schema:

Group X	Group Y
Placebo, 4 weeks	Placebo, 1 week
Marplan, 3 weeks	Marplan, 6 weeks
Marplan, 3 weeks	Placebo, 3 weeks
Placebo, 4 weeks	Marplan, 4 weeks

An interne was assigned to study the patients throughout the investigation and instructed—for each three-week period— to perform a physical examination and to complete an evaluation by a modified L-M Fergus Falls Behavior Rating Scale and by a special 100-item behavioral rating scale for mental patients (17). In addition, electrocardiograms and chest roentgenograms were obtained and urinalyses, complete blood counts and liver function tests carried out at the end of each period. Blood pressures were checked several times during each test period. The interne did not know in which group the patient belonged nor the tablet the patient was receiving; neither was this information given to the physician in charge who made rounds and recorded his impression of the patients. The nurses and orderlies familiar with the patients also recorded their impressions.

During the initial placebo periods several patients either died or refused to continue taking the pills because they felt they were not being helped. Shortly after the study was begun 2 women were added to Group Y. Group X finally contained 15 patients (males) and Group Y 19 patients (17 males and 2 females), making a total of 34. The average age for both groups was 72 years.

RESULTS

Clinical response

Based on clinical observation, improvement due to Marplan was noted in 22 of the 34 patients (about two-thirds). The effect of the drug on the type of patient described in the introduction is better gauged on the basis of data from overlapping groups.

Thus of the 22 patients with depression as a significant feature of their mental conditions, 18 improved during Marplan therapy.

Eight of 17 subjects with chronic brain syndrome improved, showing greater cheerfulness and activity and less apathy and depression.

Two patients with stroke improved, while 2 remained unchanged.

Of 5 patients with symptomatic arteriosclerotic hypertensive disease, 2 showed increased activity and an improved outlook on life; 3 manifested no important change.

Some of the patients became easier to motivate mentally and to rehabilitate physically. For instance, improvement took place in a 68-year-old man with a

fractured hip and a 62-year-old woman with a stroke; both were happier, less depressed and tackled their rehabilitation exercises with greater zeal and zest.

In general, the degree of improvement was more marked in the younger patients—those in their 60's with chronic illnesses which had not affected the brain too extensively. An example was a 61-year-old patient with a chronic kidney infection requiring an indwelling catheter. At the beginning of the investigation he weighed 96 pounds and was very depressed. During the first Marplan period he lost his depression and his appetite improved. Within the first six weeks of Marplan therapy his weight rose to 104 pounds. He became more interested in his environment and began to draw, play cards, and become more curious about his own condition and blood pressure. He also started going outdoors.

Another interesting case was a 67-year-old chronic alcoholic who was admitted with amnesia concerning both his identity and home. At first he had to be restrained, but after being treated with Marplan he began to recollect more of his past and gradually remembered who he was and from whence he came, so that we were able to notify his family. With Marplan therapy he became much more friendly and cooperative, but at the end of the placebo period he had to be restrained and at times became confused and lost his memory. When Marplan was restarted at his request, he improved again and later returned home.

Blood pressure

No significant blood pressure changes were noted in these patients during either the Marplan or the placebo periods. The average blood pressure in Group X was 132/74 mm. Hg during the combined placebo periods and 127/67 mm. during the combined Marplan periods. The average blood pressure in Group Y was 139/79 mm. during the combined placebo period and 142/75 mm. during Marplan therapy. In some patients receiving Marplan, the blood pressure dropped a few points; in others it rose. The average blood pressure for groups X and Y at different periods of medication are illustrated in Figure 1. Although there was a tendency toward lower blood pressure in Group Y during Marplan therapy, no dangerous drop in blood pressure occurred in any of the patients.

Laboratory data

A drop in the hemoglobin level of greater than 1 Gm. per 100 ml. was observed in 21 patients after the first period of Marplan therapy; in 1 patient the hemoglobin level rose, and in 12 no important changes occurred. The cause of the lowering is not clear and this effect has not been reported in other studies with Marplan. However, the level was lower in both groups at the end of the study; the average for Group X was 12.5 Gm. per 100 ml. (after four weeks of placebo) and for Group Y it was 13.2 Gm. per 100 ml. (after four weeks of Marplan). It is therefore likely that the initial levels were falsely high because of an unexplained error in laboratory techniques.

There were no significant changes in the white blood cell and differential counts, urinalysis findings (including urobilinogen), electrocardiograms, chest roentgenograms, and the results of liver function tests (including serum bilirubin, thymol turbidity and serum transaminase).

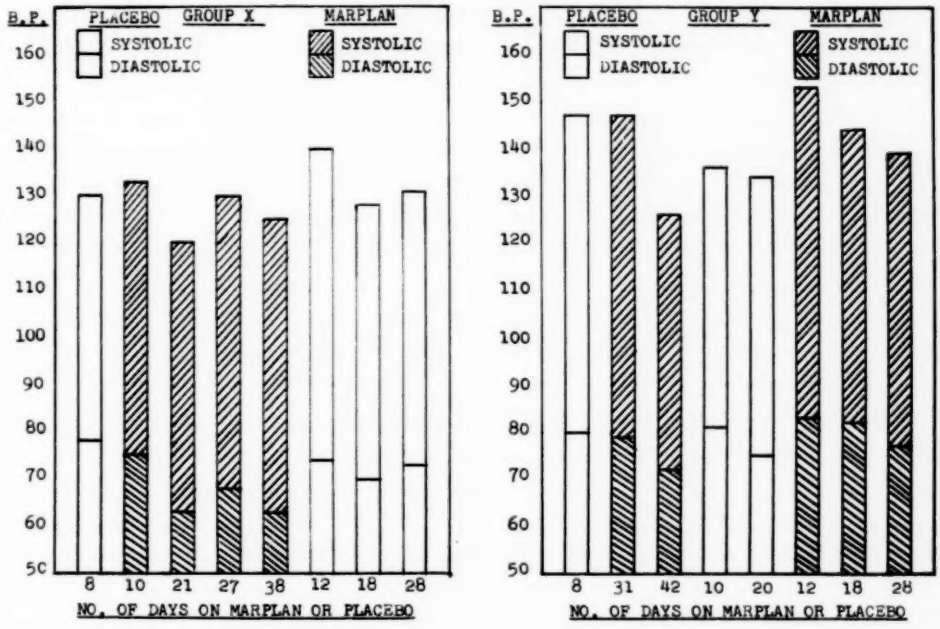

FIG. 1. Average blood pressures for groups X and Y during various periods of Marplan therapy and placebo administration.

Deaths

Two deaths occurred during the course of this investigation. No autopsies were performed.

The first patient was a 60-year-old man with complete paralysis of both lower extremities secondary to a ruptured disc. He had been progressing satisfactorily for one month under treatment with the amine oxidase inhibitor (Marplan), when he died suddenly. His blood pressure had been normal and he had had no complaints during this period. The probable cause of death was pulmonary embolism.

The second patient, a 74-year-old man, had an indwelling catheter and suffered from recurrent urinary infections. Two days after Marplan therapy was started, it was noted that he had a fever which ran intermittently. He gradually became comatose and died two days later, probably from renal causes.

No other deaths occurred and these two apparently could not be attributed to Marplan. These debilitated, elderly patients with physical complications and disease frequently die suddenly in our wards, as indicated by the deaths that occurred during the first placebo period of the study.

Behavioral rating

Ward adjustment and social behavior rating scales were used as a means of objective assessment of any alterations in the areas of self-care, orientation, cooperation, communication and socialization, psychotic behavior and reaction to environment. A number of patients who showed clinical improvement of depression also had higher scores in the tests after therapy. Nevertheless, in this

TABLE 1

Results with Shatin-Freed Behavior Rating Scale

	Mean*	Range
Group X		
Placebo	45.5	27–86
Drug	46.1	28–85
Drug	47.2	24–80
Placebo	49.4	29–83
Group Y		
Placebo	51.6	33–74
Drug	51.9	32–77
Placebo	51.8	32–80
Drug	53.6	29–81

* The means were non-significantly different from one another.

group of patients, heavily weighted with advanced senile chronic brain disease, no statistically significant changes in group behavior were noted during drug or placebo therapy in the areas tested.

Changes from original scores on the modified L-M Fergus Falls Behavior Rating Scale (maximum of 45 points) were negligible, with a statistically non-significant average gain of 1.3 points at the end of the Marplan periods.

On the Shatin-Freed Behavior Rating Scale for Mental Patients (17) the highest possible score was 98 (two items were omitted). Employing the statistical technique of analysis of variance, which allows for the detection of significant variance in scores attributable to identifiable factors, the factors of: 1) drug *vs.* placebo, and 2) X method of administration *vs.* Y method were analyzed. No significant variation in test scores attributable either to drug, placebo or method was revealed. The variation in scores appeared to be relatively random and due to chance factors, and it is reasonable to conclude that neither the drug nor the method of administration had any appreciable effect on behavior (as measured by the rating scale) in the two groups. It is possible that different results would have been obtained if a non-medicated control group of patients had been included. Average (mean) scores and the range of scores for each medication period by groups are listed in Table 1.

DISCUSSION

Even though group behavior as scored on rating scales did not change significantly, certain effects of Marplan as used in a double blind study are worth emphasizing.

1. Although there is almost universal recognition of the hypotensive action of amine oxidase inhibitors, this was not evident from our data. Otherwise there would have been a consistent lowering of the group average blood pressure during each period of Marplan administration. Figure 1 shows that this did not occur.

2. The reduction in hemoglobin concentration in 21 patients is at odds with the findings of other studies, and there is no pharmacologic basis for expecting such an effect. It would seem to be most reasonably explained by a consistent factor of error in the initial laboratory measurements.

3. The double blind technique may be self-defeating when a clinical response is evident with unknown medication A, but not with unknown medication B. In some of our patients, definite clinical improvement could be established during the period of Marplan therapy. In others the change was so subtle that we were not aware of the improvement until they had been returned to the placebo therapy with consequent deterioration in their physical and mental conditions. Yet at the time of the observations we did not know which pills these patients were receiving.

For example, an 83-year-old senile, irrational patient with chronic brain syndrome appeared to be failing during the latter part of the investigation. He was eating poorly, was no longer attentive and was unpleasant and tired. Deterioration was so rapid that medication was discontinued in order to avoid any possible complications. Upon identifying his medication, we discovered deterioration had started while he was receiving placebo after having received Marplan for six weeks. In several other instances similar mental deterioration was noted under similar circumstances.

Thus, although theoretically the observer is unbiased because he does not know which medication is being given, the clinical response of certain patients to one type of pill may be so obvious that it is equivalent to the unintended breaking of the code, and with a change from one medication to the other the observer may tend to look for, and even "find" effects that are not present.

4. This study clearly demonstrates that the brain of the senile patient will respond like that of a younger person to the administration of a monoamine oxidase inhibitor. Marplan can influence the aged brain, healthy or diseased, and alter the psychologic affect of elderly people despite their years. The aged person's response to this psychic energizer is unpredictable. In some patients the drug improved mood, behavior and cooperation, whereas in others it activated latent grouchiness, irascibility and bellicosity. This variable action on the arteriosclerotic senile brain is not unexpected, since the drug must act on cerebral areas with different levels of function due to age and organic disease. In addition, the patient's underlying basic personality must also determine whether he will become a philanthrope or misanthrope under the influence of a drug like Marplan.

SUMMARY AND CONCLUSIONS

A double blind study is presented of the effect of isocarboxazid (Marplan), an amine oxidase inhibitor, on 34 permanent residents of an old age home. Improvement in mood and attitude was observed in 22 subjects, including 18 in whom depression had been a prominent factor.

The scores on two behavior rating scales revealed no statistically significant changes in group behavior due to drug, placebo or method of administration. With the exception of an apparent lowering of the hemoglobin level, which may have been a laboratory artefact, isocarboxazid seemed to be an unusually safe

amine oxidase inhibitor. No adverse effects on blood pressure or liver function were observed.

Although the group behavior scores indicated that isocarboxazid therapy did not greatly ease the burden of care of the psychiatrically more hopeless aged residents of the Ann Lee Home, the relative safety of administration and the beneficial effects in cases of depression warrant a trial in similar old age institutions.

REFERENCES

1. Harris, R.: Clinical use of reserpine (Serpasil) in geriatrics, *Ann. New York Acad. Sc.* **59:** 95 (Apr. 30) 1954.
2. Randall, L. O., and Bagdon, R. E.: Toxicology of Marsilid and other amine oxidase inhibitors, *Dis. Nerv. System* **19:** 539 (Dec.) 1958.
3. Ayd, F. J.: A preliminary report on Marsilid, *Am. J. Psychiat.* **114:** 459 (Nov.) 1957.
4. Dooneief, A. S., and Crane, G. E.: Iproniazid as adjunct in the treatment of debilitated patients with tuberculosis, *New York State J. Med.* **57:** 3477 (Nov. 1) 1957.
5. Frantz, A. G.: Fatal jaundice associated with iproniazid (Marsilid) therapy, *J. A. M. A.* **167:** 987 (June 21) 1958.
6. Zetzel, L., and Kaplan, H.: Liver damage concurrent with iproniazid administration, *New England J. Med.* **258:** 1209 (June 5) 1958.
7. De Verteuil, R. L., and Lehmann, H. E.: Therapeutic trial of iproniazid (Marisilid) in depressed and apathetic patients, *Canad. M. A. J.* **78:** 131 (Jan. 15) 1958.
8. Darling, H. F.; Kruse, W.; Hess, G. F., and Hoermann, M. G.: Preliminary study of isocarboxazid, an iproniazid analog, *Dis. Nerv. System* **20:** 269 (June) 1959.
9. Ford, R. B.; Branham, M., and Cleckley, J. J.: Isocarboxazid: a new antidepressant drug, *Clin. Med.* **6:** 1559 (Sept.) 1959.
10. Darling, H. F.: Isocarboxazid (Marplan) in ambulatory psychiatric patients, *Am. J. Psychiat.* **116:** 355 (Oct.) 1959.
11. Oltman, J. E., and Friedman, S.: Use of Marplan in depressive states; a preliminary report, *Dis. Nerv. System* **21** (Sect. 2): 81 (March) 1960.
12. Kimbell, I., Jr., and Pokorny, A. D.: The use of Marplan in chronically depressed patients, *Dis. Nerv. System* **21** (Sect. 2): 70 (March) 1960.
13. Azima, H.; Durost, H.; Arthurs, D., and Silver, A.: The effect of Ro 5–0831/1 (Marplan) in depressive states, *Am. J. Psychiat.* **116:** 453 (Nov.) 1959.
14. Freeman, H.; Kenefick, D. P., and Rivera, M. R.: A clinical evaluation of Marplan in depressed patients, *Dis. Nerv. System* **21** (Sect. 2): 104 (March) 1960.
15. Rothman, T.: Preliminary study of the effectiveness of isocarboxazid in the depressive syndrome, *J. Neuropsychiat.* (in press).
16. Simons, R.: New antidepressant drugs, *Delaware Pharmacist* **13:** 4 (Oct.) 1959.
17. Shatin, L., and Freed, E. X.: A behavioural rating scale for mental patients, *J. Mental Sc.* **101:** 644 (July) 1955.

MODES OF PSYCHOTHERAPY IN THE AGED

JOOST A. M. MEERLOO, M.D.

New York, N. Y.*

In all psychotherapy, communication and rapport are the most important tools of treatment. The prescribing reflex, often based on some inadvertent magic need to cure, can interrupt the patient's need for initial rapport.

Not long ago a depressed woman of 72 called at my office. She had already visited several clinics without finding relief from her unhappy feelings. After having shown me the list of the various medications she had been obliged to swallow, this sophisticated widow asked me in a slightly sarcastic tone what new miracle drug was in store for her. In so doing she indicated, between the lines, the therapy she wanted. As a matter of fact, the different clinics had been very expeditious and quick in their therapeutic decisions. Not much conversation—this token of real rapport—had taken place. She had gone through the diagnostic mill and come out with a prescription. The woman represented a typical case of mild arteriosclerosis cerebri, and indeed some tranquilizer had been indicated to soothe her so-called organic anxiety.

Yet, our patient was burning inside. She also had a real emotional problem but nobody had been willing to listen to her. The arsenal of effective medical magic kept getting between her and the therapeutic relationship she craved. So we decided together not to take pills and tablets, but to probe for the origin of her problems.

She was seen by me for only six weeks in twice-a-week sessions. In the very first therapeutic interview she was able to talk about her conflict with a hostile daughter-in-law who had cut her off from her grandchildren. By the second visit she could tell me that this family conflict had triggered her depression. In the meantime the omission of tranquilizers had cleared up her mind and she felt less depressed. The inner battle was centered around giving up her pride and making the first move towards her daughter-in-law for the sake of a better relationship with all those who were dear to her. Much of our later talk was about her possessive dominating feelings towards her son.

Why start my ponderings about psychotherapy in the aged with this case that responded so well to short-term psychotherapy? It shows in a nutshell several problems that arise in the therapy of elderly people. Even when there may be an organic basis for some of the psychologic troubles, the patient asks in the first place for good relationship and rapport with the therapist. Yet, on the basis of the therapist's inadvertent prejudiced attitude towards old age, this relation is often withheld behind the mask of clinical tranquilizing aptness. Three principal factors influence the negative feelings of the therapist towards the aged; these may explain the diversity of opinions about the aims of geriatric psychotherapy in the literature.

1. The traditional neurologic picture of decay of the brain in old age—the

* *Address:* 300 Central Park West, New York 24, N. Y.

arteriolosclerotic destruction and the Alzheimer degeneration of cells—makes the therapist skeptical as to whether regeneration and cure are still possible. The prejudice of hopelessness still dominates geriatric psychotherapy. Yet, we forget that regeneration belongs to life and that many wounds heal, even in the dying patient.

2. There is an unwitting revival of repressed conflicts with the therapist's own parental figures. In such an example, there was a battle between the generations in a control case. The therapist involved had to give financial help to his parents. Unwittingly his own resentment crept into his therapy of the aged.

3. In the minds of both patient and therapist there lingers an unobtrusive fear of death. That is why they both shun a close therapeutic relationship. It is, for instance, difficult for many doctors to identify themselves with the emotional troubles of the dying because they have not yet solved their own fear of growing old and their defensive relation to death.

THE IMPORTANCE OF ECOLOGIC FACTORS

The influence of the immediate surroundings is of great importance. The threat of isolation from relatives has, in old age, nearly the same anxiety-provoking impact as it has in early childhood. The threat of hospitalization or of being displaced to a nursing home is experienced by many a patient as a prelude to the great abandonment of death. The cold institutional attitude of pension plans and nursing-home schedules can be highly traumatic for persons searching for a new sense in their lives. They cling to their private possessions and their individual privacy as they cling to life. The more useless they feel, the greater their retreat into privacy and detachment.

Being aware of these pathogenic environmental factors often leads the physician to psychotherapeutic successes. Most of my insight into this problem is based on my experience with the Social Psychiatric Service of the City of Rotterdam, where in 1927 a regular home service for the psychiatric aged was established. For the city this was not only charity, it was also a means of keeping down the number of hospitalized patients; as an adjunct, the patients themselves felt much happier. Moreover, there existed in Holland an old tradition of taking care of the aged. From the time of the Middle Ages, special courtyards (beguinages) were built for the old, many of which still exist and are used as memorials to the chivalry of ancient days. These courtyards form geriatric communities within the community, usually under supervision of a social worker, but nevertheless with an emphasis on privacy. A group of elderly people live there, each in his own tiny home, paying no rent or a minimum of rent. There is no rigid institutionalization or exploitation, but a return to a communal self-help atmosphere and greater security and relaxation.

We attempted to establish a comparable form of ecologic therapy for the aged with patients from the psychiatric clinic and from private practice. My oldest patients receiving regular analytically-oriented psychotherapy were respectively 72, 82 and 86 years old. Many senile and pre-senile patients usually receive some supportive psychotherapy and tranquilizing medication. Tranquilizers often have a beneficient action on the symptoms of anxiety, provided the therapist is

aware that individualized selection of medication is important. Patients not reacting to one brand may react better to another and, in old age, smaller doses than usual have to be given. Our new approach was to require the social worker in the clinic not only to receive clients at her office desk, but also to visit them in the home. In the future it will be necessary to make more use of such specialized social workers visiting the homes of the aged.

This visit to the home often did more for the lonely and suspicious senile patient than any therapeutic conversation in the clinic. For the patients who lived alone, the visit and the cup of coffee they were allowed to prepare for their visitors, signified more understanding than the psychiatric lingo. It became a new token of belonging. This is also true for private patients who threaten to become caught in their suspicions. Our society, by its rejection of the aged and by the adoration of glamorous sweet youth, unwittingly pushes older people into loneliness and detachment. This point is stressed because there are cultures in which old people receive special esteem and status. Some Oriental cultures revere the aged before their final step to their idealized ancestors, although behind this adoration stands the fear of the magic influence that the dead might have on the living.

Loneliness, even when self-chosen, is disintegrating, no matter what motivates the mental processes. Every form of psychotherapy in old age has to take this into account. For several patients we were able to find creative activities—not occupational therapy in the dry sense of the word, but normal, useful activities. It is amazing to see how this regaining of social participation not only increases the general activity of the patients but helps them to overcome memory defects. Loss of memory is a complicated psychopathologic process in which frustration and repression vie with organic causes. Sometimes the loss of memory can be a too-early masochistic acceptance of being old and debilitated. For example, a professor, a mathematician, took leave because he was too old and had lost his memory; in reality, he used his too-small pension to revel in misery and injustice.

THE TRANSFERENCE SITUATION

This leads us to investigate the extremely complicated doctor-patient relation in therapy with the aged. General rules cannot be laid down because so much is dependent upon the degree of organic failure and the neuro-possibilities for contact. After a stroke combined with aphasia, this contact will be most difficult. Yet, this lack of communication affects also the therapist's feeling of benevolence.

The doctor is more often than not, younger than the patient, and because of this he frequently represents, instead of a parental figure, one of the children of the patient. For the most part, a combination of parental and filial images is transferred to the therapist. Yet, the patient's pride about his *illusory paternal authority* is very sensitive and has to be taken seriously. Often physicians have to play the role of the listening child, even when such patients try to manipulate us like little children. Usually a short interpretation stops this acting out. The countertransference of the therapist is often more difficult to check. Treating a declining life hurts our medical narcissism and our expectations of magic cure. Again, there exists an unobtrusive rejection.

Nevertheless, when there is not such a negative countertransference, the time and patience given to older people, who feel themselves lost in a hostile world, often build a strong patient-doctor relationship. As a result, patients—even those with cerebral arteriosclerosis—experience a remarkable clearing of mental functions. The task of therapeutic communication is to break through the communicative isolation.

An important problem in psychotherapy with the aged is that there is no therapeutic indication to solve the transference purposefully. Therapy represents to the patient a substitute for the lost social contact, until he is able to make new relations again. In the clinical setting, even when the patients themselves ask for the dismissal signal, it is better to let them come back from time to time so that they may feel that contact is not lost. In their wish to be dismissed the patients often check the therapist's acceptance of them.

A medical student once asked me quizzically why we so ardently tried to treat with slow, long-lasting psychotherapy a group of patients who had no real future. I answered him: "Because psychotherapy gives them back their past." For many a patient, it is a stimulating experience to discover that one's own past can be explored in the service of today's self-understanding and renewed adjustment. The psychodynamics involved may be formulated as follows: *Those who think that they have no future must be brought back to the past in order to accept the present.* We have observed a demented patient with whom we could only have rapport by reading stories from the past and asking questions about early childhood. Yet, this token rapport with this institutionalized patient lifted her out of a depressed feeling every time.

According to the law of Ribot, in cases of senile memory defect, the latest perceptions are lost first and the codification of recent impressions is impaired, but the older memories resist the law of decay. As a matter of fact, in psychiatric psychotherapy we encounter a steady increase in childhood memories which patients try more and more to relate to actual happenings. Man's patterns of adjustment are formed in early childhood and they condition the later attitude toward the vicissitudes of aging. That is why we have to rediscover these childhood patterns. The return of memory in these patients is apparently the result of this process of renewed mnemic incorporation of the actual into the old. For this reason, repetition of the revealed memories, dreams and associations should not be avoided in the next session. Usually this results in a better temporalization of facts along the timeline. What once was confusion again becomes a sensible life history.

The ancient function of the old—informing the young by word and song about the heroic myths and wisdoms of the tribe—has been completely lost in our era of technical communications. Technique separates the generations more and more. Grandparents have difficult competition with the television screen. Therapy helps to bring back that communicative function of the older generation.

Even the psychoanalytic technique of free association is experienced by elderly patients as a true liberation from their fear of chaos, provided the therapist is is able to relate and integrate the loose pieces. The detection of determination in

what seemed chaotic to them becomes quite a new adventure for many patients. It enhances the transference and the therapeutic goal of self-acceptance. Many of our geriatric patients suffer from society's denial of love, praise and admiration, those feeders of man's self-esteem. Geriatric psychotherapy must have as an an aim the rebuilding of that self-esteem. Thus in homes for the aged the greatest possible freedom must be given. One of my patients was a woman aged 86 who ran away from such a home and preferred to live alone because she was continually treated as a child by a bossy nurse.

Analytically oriented psychotherapy helps the elderly to rediscover hidden inner resources, and thus to conquer the feelings of uselessness and boredom, those childhood-originating feelings of complete emptiness. One of my oldest patients, a former lawyer of 76 who came with tremendous memory disturbances, started to study philosophy as a new hobby. With his new-found detachment from subjective complaints he obtained a clearer grasp of the subject of logic than before. The Swiss idea of forming a university for the aged has much sense.

RESISTANCE TO THERAPY

The handling of resistance in the elderly is different than in younger people. As a result of the organic process and the anticipated departure into death, infantile passive defense mechanisms are set into action. Masochism, suspicion, pseudo-detachment and withdrawal have to be continually watched for, and the self-damaging influences explained. Yet, it would be bad strategy to stir up the patient's emotions through a continuous attempt to explore what he is unwilling or unable to communicate. Even old sexual taboos are revived in an attempt to stem the renewed onslaught of instinctive impulses. Like all defenses, the increased introspection in old age has a double character. It may be a passive masochistic defense to prove how much life has failed them, but it can also be an attempt to repair and to formulate some inner sense to a life that will be concluded in not too long a time.

In these we usually have to deal with a spontaneous breakdown of the more active ego defenses and failure of defensive systems around an overcritical superego. The therapist, as it were, has to play the role of a more benevolent superego and help the patient to feel less regretful and punishing toward himself. This is especially the case in reactive depressions and agitated depressions. We have to show our patients that they can adapt to new circumstances with less remorse and compulsiveness. A woman of 68 who had an agitated depression after the loss of her husband, who had always been a brute to her, reacted most defensively at first when I explained her constant wailing as a disguised imitation of her husband. At the next session she was more open, and spoke about the "devil" who had gotten into her. This was a first break in her tense anxiety. The so-called geriatric rigidity is only a recently acquired pseudo-defense more related to fear and reduced organic adaptation than to an old rigid system of ego defenses. Because of the weakening of the older defenses there is in many geriatric patients a better and more direct contact with the unconscious. Older patients react in a less biased way to interpretations and feel more easily relieved by

relating the actual conflicts with those of the past. Most people look back at their youth with a feeling of happiness, while denying the conflicts with which they had to face early problems.

The therapist's interpretations can be of a more intellectualizing nature than when treating younger psychoneurotics. For instance, an old lady complained of rhythmic beating and auditive hallucinations during the night. She became quiet and awed after it was demonstrated to her, as she listened through a stethoscope to her own heartbeat, that the obsessive rhythm she heard was only the circulation of the blood in her own vessels, reflected back to her from her pillow. In due course, she stopped the secondary hallucinatory distortion of an arteriosclerotic symptom.

The guided readaptation to strange body feelings and changes in the body image plays an important, supportive role in the psychotherapy of the arteriosclerotic patient. However, from time to time, we have to borrow from the pharmacotherapeutic arsenal that which understanding and catharsis cannot immediately deliver to the patient. Besides the variety of tranquilizers and cerebral stimulants, a place in therapy should be given to belladonna and scopolamine, which are frequently more effective. In pain due to cerebral arteriosclerosis, often only scopolamine will take effect. Anxious and depressed patients need a stimulant in the morning and a tranquilizer at night. However, an iatrogenic neurosis may occur, especially in old people, as a result of both compulsive hoarding of medicaments by the patient and the automatic need to prescribe by the physician. In several cases we had to take away the whole pharmacopeia that served only as a useless symbol to stave off feelings of decline and death.

THE CHANGED BODY IMAGE

The problem of medication leads us to look at the strangely changed body image in old age. It is as if many of the early infantile images of the body were returning. This is a true psychosomatic problem and causes great trouble to the internist who has to distinguish between the multiplicity of hypochondriacal complaints and the organic geriatric changes. Even without detectable neurologic changes, phantom limb sensations occur more frequently in the aged.

Because of the increase in internal warning signals in aged people, the body acquires more attention. This process often starts with the hormonal changes at the climacteric, in both male and female. The person's vital functions are severely tested. Together with the overemphasis on body function, there is increased anal hoarding as a defense against the great departure. We have to teach the patient to do well and not to look backward in the bathroom.

Then there is the delusion of being poor. This complicates a real or imagined loss of income. Usually the complaint symbolizes: "my time is short." The sense of time is out of order, and becomes more out of order if the patient becomes more isolated. The awareness of approaching death and the knowledge of the lack of future disturb all sense of continuity. Eating becomes a new ceremonial to evade death.

The partly psychologic etiology of these changes—the inner reactions to disturbed function of various organs—is emphasized because, under well-

directed therapy, many of these dysfunctions can be corrected. A lonely old woman with total time disorientation regained her sense of timing as a result of the scheduling and well-timed occupational endeavor in the old-age home. Meals and work became the new clock. Man's relation to time usually symbolizes man's relation to life and mankind.

Under the influence of different organic disturbances, the body image may undergo changes which are sometimes expressed in fantastic dreams and avoidance reactions. Cerebral hemorrhage, heart failure, hypertension, and diminishing vision may contribute to fresh outbreaks of anxiety. Meanwhile the patient regresses to a paradoxical angry masochistic defense which so often contaminates and affects the mood of the nursing personnel. The patient's anger is not merely hostility, but also a cautious testing of the therapist's acceptance. We have to teach both patients and nurse that anger usually is a mask to cover up a deeper need to be cared for. The renewed catastrophic reactions temporarily hide the more valuable part of the personality. The stubborn refusal of help is an ambivalent protest. Patients want to deny that their functions are diminishing but they accept nevertheless the spontaneously-given help.

In geriatric medicine the danger of too much emphasis on organic changes is that this may lead to the physician's denial of the psychologic reaction to the organic disturbance. True, there may exist angina pectoris and hypertension, but the symbolic meaning of the diminishing cardiac function is loss of love. That is why the therapist so often has to give guidance to the marital partner and the children as well as to the hypertensive old patient himself.

IMPORTANT PSYCHODYNAMICS IN OLD AGE

The growing avalanche of literature in the field is proof that the urge to write about the psychology of senescence is greater than the number of verifiable facts. The onset of involution and decline differs widely in many persons. We suppose that much of its beginning depends not only on the somatic constitution of the body, the decline of bodily resistance and the decrease of homeostatic capacity, but also on underlying psychic compulsions and lifelong frustrations. We are aware, for instance, how much disproportional energy is consumed by compulsive neurotic defenses; they usually lead to exhaustion and early aging.

Let us not forget that some psychologic changes in old age may be useful to the person. After all, aging and maturation go together. Though there exists a large group of elderly persons remaining anxiously and rigidly bound to tradition, with diminishing initiative and decreasing ability to adapt, there is also a group that feels free from the bonds of tradition and the conformity that their work previously imposed on them. The latter group adjusts itself more easily to the new circumstances. These people have been looking eagerly forward to their "*otium cum dignitate.*"

The literature so often mentions that the capacity for learning new skills diminishes. That is true for learning new automatic skills with complicated motoric involvements, but not for jobs involving patience and emotional investment.

Old age can be the time of ripe experience and inner wisdom if the mind re-

mains alert. We touch here on the complicated psychology of man's active interest, zest and liveliness and the more cultural problem of keeping mental functions alert. The choice of work is so important. Even a group of institutionalized demented old women woke up out of their psychic dullness when they were allowed to take part in the care of abnormal children in another pavilion.

Although the attention of older people is often directed more toward the past because there is (according to them) hardly any future in prospect, riper age may result in lessened suggestibility and a more circumscribed personality. The well known stubbornness of the aged means that they are not only difficult to convince and to argue with (though this is much easier in the therapeutic transference), but they are also difficult to persuade by simple suggestions. A secondary ego-fortification may take place when coercive suggestive forces no longer have their shattering impact.

Old age can represent mental stability and continuity, correcting the infantile ambivalence and vacillation which is so much longer-lasting in our automatized epoch. Especially in our technical world with its noisy worship of the new and the modern only because it is new we need correction by a riper attitude resulting from the wisdom of historical continuity. History has shown that the great minds have been able to bring the creative gifts to fruition at a rather late age. Technic grows in childhood, wisdom in old age.

There exist, however, specific degenerative processes of the body, in which the breakdown of functions of the cortex of the brain plays an important part. Tiny vascular accidents usually start this process. Psychic defenses break down as a result, and a return of the repressed factors is in full swing. For example, 3 elderly male patients were prosecuted because they had tried to seduce young girls. The shame and frustration they showed was even more pitiful than the abundant moral indignation of society. A diminished legal responsibility because of the organic involvement could be established; but what was more important psychologically was the fact that for years all 3 men had been looking for some medical help for their sexual confusion. One doctor told one of them that old men have no right to seek for sexual satisfaction any more. This same instinct-denying principle had caused their wives to reject them. In 2 of the 3 cases the act of giving simple sexual information—imagine, to the young boy of 68—and talking the problem over with the spouse took much of the tension away. This therapeutic understanding was also helpful in preventing the acting out of their repressed sexual prowess.

In many old people with partial regression there exists a hasty need for complete sexual gratification before death. "Now I want to have that one final orgasm I didn't get in my youth." Such an inopportune craving may lead to severe tensions and the tragic breaking up of the home when the deviation is not understood. I remember so well a church scandal that broke out when it was found that the minister had gone on a binge to a brothel. Hardly anyone thought about the tragic aspect of the situation. Here was a deeply frustrated man who had lost control after a tiny cerebrovascular incident.

The upsurge of aggressive forces in these years of diminishing ego control may

also lead to a strong inclination toward self-destruction and destruction of human relationships, especially when these inner troubles are aggravated by alcohol and drugs.

In married couples during these declining years there is often an increased morbid impact of mutual neurotic trends. Now that the children are no longer there, the parents begin to educate and mentally contaminate each other more violently. They feel that their marriage has become empty, and by seeking mutual control they try to fill this emotional vacuum. An intermarital rivalry may develop, for instance, for the love of children and grandchildren. This rivalry increases as vitality decreases. Only psychotherapy of the total environment can prevent a lot of unhappiness.

For lonely old aged people, the neighbors play a specially symbolic part; they often become the tokens of lost paternal relations, and toward them all the once-buried ambivalent feelings are revived. Usually the hostile part of the old relationship is projected onto the neighbor. The delusion of persecution by neighbors is conspicuous in senile paranoia, but lies dormant in many other senile disturbances. In this situation, the first form of mental first-aid is to break up the feeling of isolation and the vicious circle of projection, anxiety and renewed projection. A visiting schedule by either the therapist or the social worker in the home often gives back to the patient a feeling of security.

THE HIDDEN PACT WITH DEATH

Especially in the aged, an acute neuropsychosis may break out when a beloved one dies. Psychic defenses are shattered and the bereaved one wants to join the dying. The mourner retreats into morbid solitude. Yet in many dreams of the aged we can detect attempts to arrange a secret, magic pact for immortality. Returning phobic symptoms signify an attempt to escape death or hidden death-wishes. Senile claustrophobia means both escape and a pact with death. The elderly hysteromelancholic usually hides suppressed death-wishes towards the spouse who was found to be lacking. The aging person often cannot accept the reality of being mortal; his hostile death-wish toward the mate signifies a token offering to the gods: "Let him go first."

There are various symptoms ranging from passive surrender to the Reaper, to the continual flight from and denial of death. The catch phrase, "It is too late," is repeated with many variants. Insomnia results from the dread of sleeping on forever and the fear of the loneliness of death. Many a lonely, senile paranoiac selects, as it were, his own substitute-womb and burial place long before his biologic death. Gradually, these people bury themselves—as a passive surrender to death—in slovenliness and squalor. They become recluses refusing any contact with the outside world. At the same time, they are hoarding all their possessions, including money, and in the end they starve in the midst of plenty.

This final masochistic end of the recluse signifies so well what psychiatric psychotherapy has to accomplish. It has to reconstitute the contact with the outer world, it has to replace the delusion of the need for money and for more material needs with the impact of human contact and sympathy. And finally it

has to let the patient make a different pact with death, in which death neither is the enemy nor the friend, but the final acceptance of life, as Spinoza formulated it: as the love and acceptance of man's fate.

REFERENCES

BROWN, D. J., *et al.*: The Aged and Society. Madison, Wisconsin, Industrial Relations Research Association, 1951.

FERENCZI, S.: Beitrag zum Verstaendnis der Psychoneurosen des Rueckbildungs-Alters, *in* Bausteine, vol. III. Bern, Huber, 1939.

FREUD, S.: Mourning and Melancholia. Collected Papers, vol. IV. London, Hogarth, 1949.

GITELSON, M.: The emotional problems of elderly people, *Geriatrics* **3:** 135, 1948.

GOLDFARB, A. J.: Contributions of psychiatry to the institutional care of aged and chronically ill persons, *J. Chronic Dis.* **6:** 483, 1957.

GROTJAHN, M.: Some analytic observations about the processes of growing old, *in* Psychoanalysis and the Social Sciences, ed. by G. Róheim. New York, International Univ. Press, vol. 3, 1951.

HERKIMER, J. K., AND MEERLOO, J. A. M.: Treatment of mental disturbances in elderly women, *Social Casework* **32:** 1951.

KAUFMAN, M. R.: Psychoanalysis in late life depressions, *Psychoanalyt. Quart.* **6:** 308, 1937.

KRAPF, E. E.: On ageing, *Proc. Roy. Soc. Med.* **46:** 957, 1953.

MEERLOO, J. A. M.: Contribution of psychoanalysis to the problems of the aged, *in* Psychoanalysis and Social Work, ed. by M. Heiman. New York, International Univ. Press, 1953.

RANDALL, O. A.: Sociological aspects of aging, *J.A.M.A.* **147:** 1325, 1951.

SCHILDER, P.: Psychiatric aspects of old age and the aging, *Am. J. Orthopsychiat.* **10:** 62, 1940.

STERN, K.; WILLIAMS, G. M., AND PRADOS, M.: Grief reactions in later life, *Am. J. Psychiat.* **108:** 289, 1951.

GOLDFARB, A., AND TURNER, H.: Psychotherapy of aged persons, *Am. J. Psychiat.* **109:** 916, 1953.

WAYNE, G. J.: Modified psychoanalytic therapy in senescence, *Psychoanalyt. Rev.* **40:** 99, 1953.

WOLFF, K.: Group psychotherapy with geriatric patients in a mental hospital, *J. Am. Geriatrics Soc.*, **5:** 13, 1957.

Abstracts of Current Literature

STUDIES ON THE BIOLOGIC CHARACTERIZATION OF HUMAN GONADOTROPINS. IV. COMPARISON WITH TWO NEW PREPARATIONS OF HPG FROM THE URINE OF POSTMENOPAUSAL WOMEN.

Albert, A., and Derner, I. *J. Clin. Endocrinol. & Metab.* **20:** 858 (June) 1960.

One of the new preparations was made using carbunite (HMG-J-5) and another by kaolin zeolite adsorption (Pergonal). By preliminary assay, HMG-J-5 contained 23.6 rat units per mg. and Pergonal 18.1 rat units per mg. Multiple-dose assays for each substance, using the simultaneous response of the ovary and uterus of the immature rat, agreed with each other, and the slopes of the ovarian and the uterine response and the dose ratios at the control level were the same as those in similar assays of HPG from postmenopausal women prepared from urine by the kaolin-acetone method. Thus, no difference in biologic nature could be detected in postmenopausal HPG when prepared by these three methods of extraction and purification.

SUBLINGUAL ERYTHROL TETRANITRATE IN THE TREATMENT OF ANGINA PECTORIS. EFFECT OF VARYING THE DOSE AND RATE OF ADMINISTRATION.

Altman, G. E.; Riseman, J. E. F., and Koretsky, S. *Am. J. M. Sc.* **240:** 66 (July) 1960.

Powder and tablets of erythrol tetranitrate disappeared more rapidly and uniformly from the sublingual region than from the buccal pouch, absorption requiring about twenty minutes less. Despite a rapid dissolution time, the drug in both forms had a prolonged beneficial effect upon sublingual administration to patients with angina pectoris as judged by an increase in exercise tolerance. Doses of 30, 45 and 60 mg. were not effective in patients who failed to respond to 15 mg. Side-effects reported by several patients consisted of transitory burning of the oral mucosa at the site of contact, which was less severe when tablets with a rapid dissolution time were used, headache after 15 mg., and mild dizziness, lightheadedness or faintness after a 15-mg. tablet of ethyrol tetranitrate with rapid dissolution time. A moderate decrease in systolic blood pressure occurred in some of the patients after sublingual administration of erythrol tetranitrate with rapid dissolution time. The 5-mg. doses were less likely to cause undesirable side-effects and were sometimes as effective as doses of 10 or 15 mg.

DERMAL CHANGES FOLLOWING APPLICATION OF CHEMICAL CAUTERANTS TO AGING SKIN. SUPERFICIAL CHEMOSURGERY.

Ayers, S., III. *A.M.A. Arch. Dermat.* **82:** 578 (Oct.) 1960.

Applied to small areas of the face and neck, liquid phenol lessens wrinkles and actinic skin changes and may be used in conjunction with surgical planing. It also may have some prophylactic value against the development of precancerous actinic keratoses and skin cancer. The clinical and histologic changes following the application of phenol resemble those following abrasion. The epidermis regrows and new dermal connective tissue forms just beneath it. Liquid phenol penetrates to a depth of 0.3 to 0.4 mm. The area treated should not exceed 8 to 10 cm. and applications should be spaced several days apart. The patient must be checked by urinalysis and testing for the presence of phenol in the urine. As an adjunct to surgical planing, phenol application is useful in technically difficult areas as

around the eyes. When done for cosmetic purposes, care must be exercised in blending treated with untreated areas. Later work has shown that 25 to 50 per cent trichloracetic acid is preferable to phenol when an extensive area is to be subjected to superficial chemosurgery. It avoids an excessive cauterant effect and also the hazards of phenol absorption.

NECROSIS OF THE COLON FOLLOWING RESECTION FOR ABDOMINAL AORTIC ANEURYSMS.

Bernatz, P. E. *A.M.A. Arch. Surg.* **81:** 373 (Sept.) 1960.

The case reports of 4 patients who died illustrate the problems of adequacy of collateral circulation after sacrifice of the inferior mesenteric artery along with the distal aorta in patients with aortic aneurysms. Ischemia of the colon can occur after such an operation without fatal consequences but measures designed to avoid it should be taken. Usually the inferior mesenteric artery cannot be saved, but it should be ligated adjacent to the aorta in order not to interrupt an arterial arcade formed by a branching left colic artery. Efforts should be made to maintain direct arterial flow into the internal iliac arteries, and endarterectomy of the hypogastric arteries may improve the flow of arterial blood to the colon. The maintenance of preoperative blood pressure levels is important to prevent the progression of borderline ischemia to infarction and necrosis of the bowel. Preoperative administration of antibiotics might help to avoid infarction and necrosis of colons that become ischemic. Postoperative recognition of significant ischemia of the colon is difficult because pain and discomfort may be lacking. Patients observed have had hypotension, unusual temperature elevation, and thereafter abdominal distention. Roentgenograms of the abdomen have showed distention of the large and small bowel, and the ischemic bowel may be distended. Diarrhea and tenesmus, particularly in the presence of persistent ileus are likely to be an indication of ischemia of the colon. When ischemia is suspected, proctoscopic examination will prove valuable, although interpretation may present difficulties since it is possible for the colon to remain viable while the mucous membrane becomes necrotic. However, correlating ischemia with signs of a nonviable bowel may lead to early surgical treatment with a better chance for survival of the patient.

THE MYOPATHIES OF LATE ONSET.

Brain, R. *Schweiz. med. Wchnschr.* **90:** 904 (Aug. 20) 1960.

The muscular disorders of adult life include 1) polymyositis (dermatomyositis or neuromyositis when the skin and peripheral nerves, respectively also are affected), 2) myopathy associated with other collagen diseases (scleroderma, disseminated lupus erythematosis, periarteritis nodosa, rheumatoid arthritis, psoriatic arthropathy), 3) sarcoidosis, 4) myopathy associated with thyroid disorders (thyrotoxicosis, myxedema), 5) exophthalmic ophthalmoplegia (which may occur alone or in association with myasthenia gravis; thryotoxic myopathy sometimes involves the ocular muscles), 6) myasthenia gravis, 7) myopathy in miscellaneous endocrine and metabolic disorders (acromegaly, Addison's disease, Cushing's disease, and aldosteronism), 8) carcinomatous myopathy, 9) heredofamilial myopathy of late onset, 10) myohemoglobinuric myopathy, and 11) cryptogenic myography. The histologic changes of sarcoidosis may sometimes be seen in patients who do not have the clinical features of this disease. In the muscles, therefore, sarcoidosis may represent a pattern reaction that is due to more than one cause. Patients with fulminating thyrotoxic myopathy, with involvement of the bulbar muscles, may have myasthenia. The muscular weakness may respond to neostigmine and similar drugs before the thyrotoxicosis can respond to treatment. It now is recognized that carcinoma even without metastases can cause disorders of the nervous system and muscles, the latter disturbances being the less common. Both are most frequently encountered in association with bronchial asthma. Insidious in onset, the myopathy tends to affect the proximal muscles of the limbs and much less often the ocular and bulbar muscles. Myasthenic fatigability in some patients

may respond for a time to neostigmine. Carcinomatous myopathy may be intensified by the use of muscle relaxants. It shows a tendency to remit. Heredofamilial myopathies are not confined to childhood and may begin in middle age or later. The myopathy usually is of the limb-girdle type affecting the proximal muscles of the limbs first and spreading to the distal muscles and trunk. Pseudohypertrophy of muscles may be encountered in any variety of muscular dystrophy and at any age. Several cryptogenic myopathies have been noted in persons aged 40 and above. These have affected the ocular muscles alone or with other muscles, the muscles of the limbs and trunk, or only of the latter. The attack may be acute or slow, extending over a period of years. The electromyogram is characteristic of a myopathy. Histologically there are varying degrees of disintegration and degeneration of muscle fibers, phagocytosis, and inflammatory infiltration.

DEGENERATIVE COLLAGENOUS PLAQUES OF THE HANDS.

Burks, J. W.; Wise, L. J., Jr., and Clark, W. H., Jr. *A.M.A. Arch. Dermat.* **82:** 362 (Sept.) 1960.

Five patients are presented who had linear, firm plaques of the medial and lateral aspects of the hands. The lesions were bilateral and symmetrical and situated at the juncture of the palmar and dorsal skin. Histologically, the plaques were characterized by a distinctive disposition of dense collagen and elastic tissue that involved most of the reticular dermis but little of the papillary dermis and subcutis. This condition is chronic, slowly progressive, and usually without symptoms. The lesions sometimes may be yellowish or erythematous. The surface may be scaly or smooth, and glistening with telangiectasia. A shallow linear furrow at the center may extend almost the entire length of the lesion. Early cases have shown a linear array of wrinkled papules. Later lesions appear to have been formed by the fusion of plaques. The nature of the changes in the dermis is not known but the alteration suggests senile degeneration. Microscopically, the lesions show basophilic fibro-elastosis affecting most of the reticular dermis. The majority of patients affected have advanced actinic degeneration of the exposed skin.

GRANULOMATOUS ORCHITIS.

Capers, T. H. *Am. J. Clin. Path.* **34:** 139 (Aug.) 1960.

Reports of 2 cases of granulomatous orchitis are added to 37 appearing in the literature. In one case there was a small nodule with pain in the testis which was tender to touch but not enlarged. In the second patient, the testis was enlarged and firm. Neither patient had evidence of vascular occlusion, a tuberculous process, or other systemic disease. Each fared well after orchiectomy. Microscopically the testis showed intratubular granulomas with interstitial fibrosis and infiltrations of lymphocytes and plasma cells. Spermatozoa were demonstrated in the granulomas by means of the Putt modification of the acid-fast technic. Available evidence indicates that the granulomas are produced by a reaction of sperm and tissue, but the way in which the spermatozoa reach the stroma has not been determined. Possibly a degenerative process is the starting point for the lesion. This is suggested by the occurrence of granulomatous orchitis at approximately the same age (63; 65) in the patients reported and in middle and older age persons reported by other investigators, by a history of inflammation in one of the patients reported, and by the lack of a traumatic incident in the other.

TRIMEPRAZINE AGRANULOCYTOSIS. REPORT OF A CASE.

Clendenning, W. E.; Kress, M. A., and Rauschkolb, E. W. *A.M.A. Arch. Dermat.* **82:** 533 (Oct.) 1960.

Agranulocytosis occurred in an elderly woman with pemphigus vulgaris and severe pruritus who received 50 mg. of trimeprazine in one course and 250 mg. in a second course of eighteen days. The clinical course and laboratory findings resembled those in the recorded

cases of phenothiazine-induced agranulocytosis. The reaction could not be attributed to phenobarbital, which the patient tolerated well. The white blood cell count returned to normal and neutrophils reappeared when trimeprazine was discontinued. The author points out that the incidence of agranulocytosis in elderly women receiving long-term therapy with phenothiazine derivatives may be close to 1:150 and that the sex predilection in the older age groups appears to favor women in the ratio of 6:1. Until there is more definite information as to the incidence and the sex and age predilection, care should be exercised in using trimeprazine for more than a short period in women over the age of 40 years. The mechanism for the development of agranulocytosis has not been determined but it probably is not allergic. Other possibilities are a selective competition or depletion of an essential biochemical or enzyme system, or a relation to sex steroids. Treatment consists of the administration of antibiotics, regardless of whether an infection appears to be present, and general supportive measures. Steroids have little effect.

THE TRANSVERSE DIAMETER OF THE HEART IN OLDER PEOPLE.
Cowan, N. R. *Brit. Heart J.* **22:** 391 (June) 1960.

Measurements of the transverse diameter of the heart are presented in persons aged 60 to 79 years, using roentgenograms of the chest and data on body weight, height, chest diameter, and arterial blood pressure with the intention of determining the relation of heart diameter to these factors and the efficacy with which it can be predicted from a knowledge of these variables in healthy elderly persons. The average heart diameters were found to be alike for men and women aged 60 to 69 years, but in the next decade the heart diameters for men averaged 0.4 cm. more than for women. The absolute variability of heart diameter (measured by the standard deviation) was equal in the sexes, showed no change with age, was less than that of such attributes as body weight and blood pressure, and comparable to the value of 1.09 noted previously (1926, Hodges and Eyster). The relative variability of heart diameter (measured by the coefficient of variation) was alike for the sexes, showed no change with age, was less than that for weight and blood pressure, and was greater than that for chest diameter and height. The approximate relative variability of 8.9 for the heart diameter was moderate. Since the weight and arterial blood pressure vary more, the use of the heart diameter as a clinical index cannot be criticized on the basis of excessive variability in different subjects. The transverse diameter of the heart is significantly related to body weight, height, chest diameter and arterial blood pressure, but most appreciably to body weight and transverse diameter of the chest. Multiple regression equations predicting the transverse diameter of the heart in terms of the two most important variables indicate that in any accurate decision on cardiac enlargement, it is essential to take into account body weight and chest diameter.

LA CRÉATINE-KINASE SÉRIQUE DANS LE DIAGNOSTIC DE L'INFARCTUS MYOCARDIQUE (SERUM CREATINE KINASE IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION).
Dreyfus, J.-C.; Schapira, G.; Resnais, J., and Scebat, L. *Rev. franç. études clin. biol.* **5:** 386, 1960 through Ciba Literature Review **5:** 241, 1960.

The determination of serum enzyme activity furnishes valuable information as to the existence of myocardial necrosis but such tests as a rule have the disadvantage of being nonspecific. Pulmonary infarction, various diseases of the liver, and hemolytic processes may falsify the results. However, the concentration of one enzyme, creatine kinase (C.K.) is 10 to 20 times higher in skeletal muscle and in the myocardium than in other organs. Since erythrocytes contain virtually no creatine kinase, the test is not affected by hemolysis. Investigation of this enzyme in various heart diseases yielded the following results: 1) In cases of myocardial infarction with electrocardiographic changes indicative of necrosis, the C.K. and glutamic oxalacetic transaminase (G.O.T.) tests were of aid diagnostically. C.K. values became pathologic as early as G.O.T. values, but returned to normal more promptly. 2) In cases of anginal pain without electrocardiographic signs of necrosis, the

changes in C.K. and G.O.T. ran parallel. 3) In heart diseases not of coronary origin, C.K. activity usually remained normal. 4) In 4 of 9 patients with severe heart failure or pulmonary embolism, the G.O.T. level rose while that of C.K. did not. At necropsy, performed in 2 cases, no structural changes were found in the myocardium. Initial investigations have therefore shown that the C.K. test gives better results than the G.O.T. test in the diagnosis of muscular lesions, particularly of the myocardium.

ENDOCRINOLOGIC AND METABOLIC EFFECTS OF 17α-METHYL-19-NORTESTOSTERONE IN WOMEN.

Feldman, E. B., and Carter, A. C. *J. Clin. Endocrinol. & Metab.* **20:** 842 (June) 1960.

Endocrinologic and metabolic effects of 17α-methyl-19-nortestosterone (17-MNT) and testosterone propionate (TP) were determined in 40 castrated or postmenopausal women with advanced metastatic carcinoma of the breast. In patients receiving 17-MNT there was retention of fluid, virilization and withdrawal uterine bleeding. A significant fall in the level of serum protein-bound iodine occurred early in therapy, associated with a decrease in thyroxine-binding protein and an increase in the basal metabolic rate. The level of serum cholesterol increased to abnormal values in patients treated eight weeks or longer. The urinary excretion of 17-ketosteroids and of 17-hydroxycorticosteroids fell significantly, but plasma 17-hydroxycorticosteroid levels were unchanged. Urinary gonadotropin excretion was suppressed. Serum bilirubin concentration rose to abnormal values in all patients receiving more than 4,200 mg. of 17-MNT, but there was no change in the results of other routine liver function tests. Apart from a decrease in the level of serum citric acid, there was no alteration in the chemical constituents of either blood or urine. Patients receiving TP showed less fluid retention and greater virilization. The fall in the level of serum protein-bound iodine with TP occurred later and was of lesser magnitude than that observed with 17-MNT. The urinary excretion of 17-ketosteroids increased, but urinary and plasma 17-hydroxycorticosteroids were unchanged. Urinary gonadotropin excretion was suppressed. Hypokaliemia and hypercalcemia occurred in 1 subject each. (Authors' abstract.)

THE USE OF TRIPARANOL TO LOWER SERUM CHOLESTEROL.

Goyette, E. M., and Elder, J. C. *Am. Heart J.* **60:** 536 (Oct.) 1960.

Triparanol (MER-29) was given in a dosage of 250 mg. daily for one to four months to 64 patients, 54 of whom had objective evidence of coronary artery disease. Nine patients had hypertension or diabetes, or both. Serum cholesterol levels before treatment were above 200 mg. per 100 ml. in all except 1 patient in whom the level was in the 150–199 range. Two patients had serum cholesterol levels above 500 mg. per 100 ml. Treatment was discontinued in 1 patient because of nausea and vomiting, and in another because of giant urticaria. One patient died during therapy, presumably of coronary artery disease. Two were lost to follow-up. The drug lowered serum cholesterol concentration in 59 patients (88 per cent), the average drop being 74.4 mg. per 100 ml. Seven patients did not maintain their improvement during continued administration. Five patients did not experience improvement until the second month of treatment. Six patients showed a small rise in the serum cholesterol level during therapy. One patient had a documented myocardial infarction during therapy. No attempt was made to determine the effect upon coronary artery disease. A longer period of evaluation will be necessary to assess the efficacy and toxicity of triparanol.

AN AMINE OXIDASE INHIBITOR IN ANGINA. A PRELIMINARY STUDY.

Halprin, H. *Angiology* **11:** 348 (Aug.) 1960.

Marplan, or 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine, was given in daily dosages of 15 to 40 mg. to 15 patients with angina pectoris associated with coronary insufficiency and 2 with palpitation and chest pain from effort, considered to be the result of

neurocirculatory asthenia. Adjuvant therapy as required was continued. Anginal symptoms were relieved in 14 of 17 patients. The nitroglycerin requirement was eliminated in 10 of 12 patients and reduced in 2 others from large numbers of tablets to one to three daily. With 1 exception, there was no significant improvement in the electrocardiograms. In the exceptional case, improvement occurred within six months in an extremely anxious patient with severe mitral insufficiency in addition to coronary insufficiency. Complicating factors were present in the 3 patients not relieved by Marplan. Side-effects in 6 patients consisted of constipation, burning tongue, dry mouth and throat, huskiness of the voice, mild dizziness, headache, aching arms and legs, and pruritus. In 1 other patient, fatigue in the legs and ankles, jerking forward of the legs or arms, and inability to complete the sex act disappeared upon reduction of dosage from 30 mg. to 15 mg. per day. The drug had no deleterious effect upon concomitant anticoagulant therapy.

ELECTROCARDIOGRAPHIC FINDINGS IN 67,375 ASYMPTOMATIC SUBJECTS. X. NORMAL VALUES.

Hiss, R. G.; Lamb, L. E., and Allen, M. F. *Am. J. Cardiol.* **6:** 200 (July) 1960.

A detailed analysis was carried out on 6,014 normal electrocardiograms obtained from asymptomatic healthy men examined for flying status with the U. S. Air Force. These records were drawn by a random process, approximately 1,000 for each five-year age group of the adult age range. The age of the subjects ranged from 16 through 58 years. The height ranged from 62 to 77 inches; there was no apparent variation with age. Weights varied from 100 to 269 pounds. The older age groups showed a marked increase of weight for height (relative weight). The heart rate varied from 39 to 129 beats per minute with a slight increase of rate in the older age groups. P-wave duration ranged from 0.06 through 0.15 second with a median of 0.11 second. The range of P-wave amplitude was from 0.05 through 0.35 mv. P axis in the frontal plane ranged from −30 through +90 degrees, with 95 per cent of records falling between +15 and +75 degrees. There was no apparent variation between age groups for any of these determinations. The range of the P-R interval was 0.10 through 0.20 second; the median was 0.16 second (A value of 0.20 second was considered the upper limit of normal.) The Q-T interval varied from 0.24 through 0.47 second, with a median of 0.38 second. There was little variation between age groups. The Q–U interval varied from 0.40 through 0.71 second, with a median of 0.56 second. There was some increase in this value in older age groups. The QRS duration ranged from 0.05 to 0.11 second, with a median and mode at 0.08 second. The incidence of QRS durations above 0.10 second was low. The duration of the R wave in lead V_2 ranged from zero through 0.06 second, with a median at 0.03 second; the duration of the S wave in lead V_2 varied from 0.01 through 0.08 second, with a median at 0.05 second. The QRS axis in the frontal plane ranged from −90 through +120 degrees, with few subjects at both extremes. There was a shift to the left of the QRS axis with each older age group, independent of QRS amplitude and body weight changes. QRS transitions were found in all six precordial leads, with the majority (91.6 per cent) in leads V_2 through V_4. There was little variation between age groups in the distribution of QRS transitions. The T axis in the frontal plane ranged from −15 through +90 degrees, with few subjects at both extremes. The mode was +45 degrees. There appeared to be some leftward rotation of the T vector in the frontal plane in the older age groups. The T transition in the transverse plane was almost invariably near lead V_1. The mean spatial QRS-T angle ranged between zero and +139 degrees, with 96 per cent of the series falling below +70 degrees. An S–T segment vector in the frontal plane as indicated by S–T segment elevation was noted in approximately 25 per cent of the series. There was a slight decrease in the incidence of detectable S–T segment elevation in the older age groups. The vector for S–T interval was, for the most part, between +60 and +90 degrees, and the greatest amplitude of S–T segment elevation ranged between 0.05 and +0.25 mv., with the majority in the range of 0.05 through 0.10 mv. Only 8.8 per cent of the series had no S–T segment elevation in any precordial lead. The greatest amplitude in any precordial lead ranged between 0.1 and 0.5

mv., with a general reduction in the incidence of the higher amplitudes in the older age groups. As for Q waves, there were few records with Q waves of 0.04 second duration, and all of these were in lead III. Q waves of lesser duration were common. Q waves in leads I and aVL were not as frequent as those in leads II, III and aVF, but were found in association with vertical and horizontal QRS axes about equally. Q waves in leads II, III and aVF were rarely associated with horizontal QRS axes. The P–R interval minus the P-wave duration value was calculated for all records; approximately 10 per cent of subjects had an isoelectric P–R segment of 0.03 second or less. QRS amplitude was determined by vector methods. The correlation coefficients for QRS amplitude, age, QRS axis, and body weight were computed. It was found that measurable QRS amplitude, whether considered in the frontal or transverse planes or spatially, tends to decrease from the younger to the older age groups regardless of the effect of QRS axis or body weight changes. Body weight and QRS amplitude were not related. It is proposed that serial electrocardiograms may become a means of assessing the aging process of the heart. T-wave amplitude was analyzed similarly to QRS amplitude and found to decrease in the older age groups. The incidence of a terminal QRS vector creating an S_1S_2 and $S_1S_2S_3$ pattern was determined; 15 per cent of all records showed the former and 24 per cent showed the latter. These patterns represent minor normal variations of intraventricular conduction. The ratio of the amplitude of the R to the S wave in leads V_1 and V_2 was determined and found greater than 1 in 0.7 per cent and 8.5 per cent of records, respectively. (From authors' summary.)

BRIEF OBJECTIVE MEASURES FOR THE DETERMINATION OF MENTAL STATUS IN THE AGED.

Kahn, R. L.; Goldfarb, A. I.; Pollack, M., and Peck, A. *Am. J. Psychiat.* **117:** 326 (Oct.) 1960.

Data are presented on a random sample of 1,077 persons residing in homes for the aged, nursing homes and in state hospitals, who were 65 years of age or over at the time of first admission. Each person was examined by a psychiatrist using a standard interview technique, and by a psychologist who administered two brief tests: the face-hand test, and a 10-item questionnaire testing orientation and recall of personal and general information. The results of both tests were highly related to psychiatrists' clinical evaluations of the presence and degree of chronic brain syndrome, the presence or absence of psychosis associated with chronic brain syndrome, opinion as to certifiability, and degree of management problem. It is concluded that the face-hand test and the mental status questionnaire are valid measures for the determination of mental status in the aged, particularly for disorders associated with cerebral damage. These tests are considered to have a considerable potential clinical usefulness for rapid screening purposes. They provide an objective basis for uniformity of observation and evaluation by different observers. The brevity and objectivity of these tests make them desirable procedures for research purposes. (Authors' summary.)

ARCUS LIPOIDES CORNEAE AND ARTERIOSCLEROSIS.

Lindholm, H. *Acta med. scandinav.* **168:** 45, 1960 (Fasc. 1).

Of 1,923 patients examined for arcus lipoides corneae (Alc) 1,614 were more than 30 years of age. These were studied for a correlation between Alc and arteriosclerosis. Approximately one third (310 males and 222 females) had Alc, and 92, or about every eighteenth person, had cardiac infarction. Alc was more common in males than in females, as was cardiac infarction. The incidence of cardiac infarction as well as of Alc increased with age, and both conditions were fairly rare in patients less than 50 years old. When Alc or cardiac infarction occurred before the age of 50, it was practically always in males. No correlation was found between arteriosclerosis and Alc apart from the fact that both increased in frequency with age. In none of the age classes was any correlation found between Alc and arteriosclerosis. (From author's summary.)

URIN-ALDOSTERON BEI HERZPATIENTEN, DIE RESISTENT GEGENÜBER QUECKSILBERDIURETIKA WAREN (URINARY ALDOSTERONE IN CARDIAC PATIENTS RESISTANT TO MERCURIAL DIURETICS).

Malamos, B.; Moiras, K., and Levis, G. *Münch. med. Wchnschr.* **102** (17): 827, 1960; through Ciba Literature Review **5:** 242, 1960.

It is well known that patients with cardiac edema do not always respond to mercurial diuretics with an adequate flow of urine. Frequently, urinary secretion is reduced or anuria develops. Aldosterone in the urine was determined before and after the administration of a mercurial diuretic in 6 patients suffering from heart failure with decompensation and edema. The patients were resistant to mercurial diuretics used in their treatment, and their body weight had increased. Following discontinuation of the mercurial diuretics, digitalis was given. This led to improvement in the patients' condition and edema diminished. Simultaneously a decline was noted in urinary aldosterone levels, which previously had been elevated. These observations suggest that the increased retention of sodium and water in cardiac patients is due to increased secretion of aldosterone. Restoration of normal circulatory conditions by means of digitalis is accompanied not only by a rise in the secretion of urine and chloride, but also by a decline in urinary aldosterone levels. The increase in aldosterone observed in patients who are resistant to mercurial diuretics may therefore account for the untoward side-effects of these drugs when they are administered before satisfactory circulatory conditions have been achieved by means of digitalis therapy.

ADJUSTMENT OF EIGHTY DISCHARGED GERIATRIC-PSYCHIATRIC PATIENTS.

Manson, M. P., and Enguist, C. L. *Am. J. Psychiat.* **117:** 319 (Oct.) 1960.

In this follow-up study, the mean age of 80 discharged geriatric-psychiatric patients was 62.3 years. The mean number of diagnoses per patient was 2. Eighty-five per cent had a psychosis, 35 per cent had chronic brain syndrome, 13 per cent were considered incompetent, 11 per cent had cardiovascular disease, and 8 per cent had pulmonary disease. The group had spent an average of 21.7 months in the hospital but some of them had been there for many years. Comparisons were made between this group and patients remaining in the hospital among whom there were larger percentages with chronic brain syndrome, cardiovascular disease and inactive tuberculosis. The results showed that the discharged patients were for the most part well adjusted to community living and had stayed in the home setting worked out by the hospital before discharge. They were healthier and did not require the expected medical attention that had been judged necessary. One-third were able to work (a larger percentage than anticipated) and some were gainfully employed. They made a fair adjustment to their living situation and to social activities outside the hospital. Only 7 per cent appeared to be in need of further hospitalization at the time of follow-up. The remainder were judged able to remain indefinitely outside the hospital. The death rate over a 44-month period among the discharged group was 8 per cent; the group remaining in the hospital had a death rate of 18 per cent over a 39-month period. Thus, living outside the hospital stimulated these men to lead a fuller and more productive life and reduced their medical needs. In view of these findings, resistance to moving geriatric-psychiatric patients into a home or community setting seems unwarranted in many instances, and even antitherapeutic.

ORMOND'S SYNDROME. A DISCUSSION OF THE PROBLEM AND A PRESENTATION OF THREE CASES.

Margoles, J. S., and McQueeney, A. J. *A.M.A. Arch. Surg.* **81:** 660 (Oct.) 1960.

Ormond's syndrome should be the name used until there is a better understanding of the etiology and pathogenesis of this disease process which consists of retroperitoneal fibrosis and ureteral obstruction. The fibrosis may be diffuse or segmental. It always involves the

ureteral axis, with resulting ureteral obstructive uropathy. The etiology of the disease still is indefinite. Although it is believed to be a nonspecific inflammatory process, it may be idiopathic or related to trauma or neoplasia. Some attribute it to a disturbance in lipoprotein metabolism. Pain is the most common complaint, with anorexia second. The dull, aching pain is insidious in onset and affects the lumbar region or the lower abdominal quadrants. It is not related to aggravating factors and is subject to spontaneous remission and recurrence. Nausea and weight loss may accompany anorexia. Other features may be a mass palpated in the flank, low-grade temperature elevation, elevated erythrocyte sedimentation rate, and leukocytosis. There may sometimes be anuria at the outset, and edema of the lower extremities due to lymphatic obstruction or associated with signs of thrombophlebitis. Peripheral arterial insufficiency may develop from thrombotic occlusion so that there is a complaint of claudication. The disease may escape early diagnosis and be found only when ureteral obstruction is demonstrated roentgenographically. Retrograde pyelograms may show compression of the ureter with medial deviation of one or both ureters. The results of urinalysis may be normal, or simulate those found in pyelonephritis. The disease later has features of obstructive uropathy with hydronephrosis and its sequelae. Treatment is primarily surgical and directed toward urinary diversion or drainage. If an adequate operation can be performed before irreversible renal damage has occurred, the disease may be self-limited. Emergency surgery is life-saving in some situations. The procedure usually depends upon the extent of the disease process and the urgency of treatment, and may vary from dilation of the ureter with ureteral catheterization, to ureterolysis with or without transplantation, nephrostomy, T-tube ureterostomy, or ureteral plastic procedures. The disease is often bilateral and therefore the involved kidney should be saved. Exacerbations and progression following treatment can occur, so that the prognosis is guarded. Without treatment the disease will progress to a terminal uremic state.

OS CORTICOSTEROIDES NA TERAPÊUTICA DAS RETENÇÕES VESICAIS DE CAUSA BENIGNA. NOTA PRÉVIA.

Pinto de Varvalho, A. *J. Soc. ciênc. méd. Lisboa* **124** (3): 359, 1960; through Ciba Literature Review **5:** 251, 1960.

Retention of urine due to benign causes was treated with corticosteroids, usually dexamethasone in a daily dose of 1.5 mg. Nine of the cases are described in detail. Some of the patients had an enlarged prostate, and the residual urine amounted to almost 2 liters; androgen therapy had proved unsuccessful. Dexamethasone brought about a decrease in the residual urine within a few weeks. It often was possible eventually to empty the bladder completely, and the patients were able to urinate spontaneously again and to lead a normal life. Patients who did not have an enlarged prostate and whose disorders of micturition were due to other causes also derived benefit. In some cases a permanent success was achieved, whereas in others increased residual urine developed following discontinuation of treatment. This effect may be due to the fact that dexamethasone reduces the mucosal edema in the upper portion of the urethra and thus lessens the obstruction. Dexamethasone also may tone the bladder muscles. The impression was gained that prostatic adenoma decreased in size in response to dexamethasone.

THE VASCULARIZED CARDIAC THROMBUS AS A POSSIBLE VICARIOUS SOURCE OF BLOOD SUPPLY IN ISCHEMIC HUMAN HEARTS.

Rodriguez, F. L.; Robbins, S. L., and Mallory, G. K. *Am. Heart J.* **60:** 168 (Aug.) 1960.

A histologic and injection study of vascularized cardiac thrombi associated with infarcts in the left ventricle of human hearts is presented and the following conclusions reached: 1) Vascular communications may form between the lumen of the left ventricle, the vessels of the organizing thrombus, and the coronary system. 2) Such communications may persist

in old thrombi. 3) Those persisting can be of substantial size, and extend as such into the coronary arterial tree. 4) These communications may serve to usher blood from the cardiac lumen to the myocardium. 5) The vascular bed of parts of the cardiac wall vicariously supplied from the lumen of the left ventricle may become sequestrated from the rest of the coronary system. (Authors' summary and conclusions.)

INGUINAL AND FEMORAL HERNIA IN THE ELDERLY PATIENT.

Strohl, E. L.; Diffenbaugh, W. G., and Nyi, S. H. *Illinois M. J.* **118:** 141 (Sept.) 1960.

The mortality rate for elective surgery in elderly patients with inguinal and femoral hernia is low, whereas death usually occurs in the case of strangulated hernia that requires emergency resection of the bowel. The incidence of incarceration is high in elderly patients. The elective repair of a hernia should not be carried out when there is excessive cough, constipation, or prostatic obstruction. Careful hemostasis and minimal trauma are requisites of the operation. Removal of the testis and spermatic cord may be advisable in order to obtain a firmer closure of the inguinal canal. Removing the cord, however, does not insure against a recurrence. In the postoperative period, elderly patients require careful observation because of the likelihood of complications. The incidence of wound infection may be higher than in a younger patient. Surgical repair was successfully performed in 98 of 100 patients of average age 75 years, 18 of whom were over 80 years of age, and 1 of whom was 99 years old. Two patients died of complications. There were 93 inguinal (6 incarcerated) and 7 femoral (all incarcerated) hernias. Involvement was bilateral in 11 of the former and recurrent in 10. Seventy-three per cent of the patients had a complicating disease. The anesthesia used was general in 64, local in 33, and spinal in 3 patients. Bilateral repair was performed in 9 patients. Resection of the bowel was necessary in 7 patients. Postoperative complications consisted of mental confusion, urinary obstruction, wound infection, wound hematoma, bowel hemorrhage, pneumonia, bowel necrosis, pulmonary embolus, auricular fibrillation, tachycardia, exfoliative dermatitis, and a flare-up of gout. Death occurred in the patients with pneumonia and bowel necrosis.

STUDIES IN PARKINSONISM: RELATIONSHIPS BETWEEN TONE AND TREMOR IN PARKINSONISM AND IN NORMALS.

Wachs, H.; Brumlik, J., and Boshes, B. *J. Nerv. & Ment. Dis.* **131:** 32 (July) 1960.

Tone and tremor were correlated in a series of normal persons and in a series of parkinsonian patients. In normal persons, tone in an extremity and tremor frequency in that extremity tend to be correlated in a direct relationship. In parkinsonism this relationship is reversed. In parkinsonism, abnormalities of tremor may or may not be associated with hypertonus. Hypertonus, however, always is associated with abnormalities of tremor of the parkinsonian type. Thus, in a qualitative sense, tremor and tone abnormalities in parkinsonism vary directly, both when measurement is objective and when it is subjective. These findings conflict with Hughlings Jackson's observations. From this study, it would appear that the phenomena of tone and tremor in parkinsonism are separable, but when present in the same patient there is mutual interaction and modification in a direct qualitative relationship. (Authors' summary.)

SIMPLE NONSPECIFIC ULCERS OF THE SIGMOID COLON.

Yates, L. N., and Clausen, E. G. *A.M.A. Arch. Surg.* **81:** 535 (Oct.) 1960.

Eighteen cases of nonspecific ulcer of the sigmoid colon previously have been reported. Case 19 is recorded here. Eleven cases occurred in men, 8 in women. The average age of the 17 patients for whom age was reported was 50.6 years. The etiology is unknown since the find-

ings in pathologic specimens have not supported the proposed theories. The diagnosis usually is not made preoperatively. Instead, a diagnosis of peritonitis or sigmoid carcinoma is likely to be made in the case of perforated and nonperforated ulcers, respectively. The most common symptom is constipation. Other symptoms have been rectal bleeding and chronic intermittent pain in the lower abdomen. At operation or necropsy, the ulcer usually is found on the anterior surface of the bowel along the antimesenteric border. There is ordinarily a single round lesion that measures 1 cm to 4.5 cm. in diameter. It is a shallow ulcer with a granulation tissue base. Perforation, which is frequent, appears as a punched-out, discrete area. Stricture is the only other complication that has been seen. Segmental resection is recommended for nonperforated ulcers. The principles of colonic surgery should be applied when the ulcer is perforated.

THE AMERICAN COLLEGE OF PHYSICIANS

Under the Sponsorship of the
Committee on Post-Graduate Courses
Will Give a Symposium on

Problems of Growth and Aging

April 11-14, 1961

The Lankenau Hospital Auditorium
City Line & Lancaster Avenues
Philadelphia, Pennsylvania

EDWARD L. BORTZ, M.D.—*Director*

ERNEST M. BROWN, JR., M.D. HENRY F. PAGE, M.D.
Associate Directors

The teaching Faculty for this Symposium is composed of the great teachers in medicine and allied sciences.

All Fellows of the American Geriatrics Society are cordially invited to attend this Symposium.

For information concerning fees and for application blanks, please write directly to:

EDWARD C. ROSENOW, JR., M.D.—*Executive Director*
The American College of Physicians
4200 Pine Street
Philadelphia 4, Pennsylvania